DEVELOPMENT AND APPLICATIONS OF ISONITRILE-BASED MULTICOMPONENT REACTIONS

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DEVELOPMENT AND APPLICATIONS OF ISONITRILE-BASED MULTICOMPONENT REACTIONS

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Multicomponent reactions provide simple and convergent paths to structurally complex products in atom-economical fashion. With the emergence of combinatorial chemistry and high-speed parallel synthesis, MCR chemistry has experienced a resurgence of interest in the past two decades. However, the application of MCRs is still largely limited by the relatively small number of such reactions.

As part of our effort to synthesize new molecular frameworks by using the "single reactant replacement" (SRR) strategy to evolve existing MCRs, we have explored the chemistry and reactivity of several α-substituted ketones (sulfonyloxy, acyloxy, azido, halo, hydroxyl and sulfonyl) in the two most utilized isonitrile-based multicomponent reactions, the Passerini and Ugi reactions.

Guided by SRR, highly convergent routes to oxazoline, β-lactam, di-*O*-acylglyceramides, and other molecular frameworks were developed. In a relative rate study, each of the α-substituted ketones underwent Passerini condensation more rapidly than the parent ketone, which was consistent with the expected enhancement of carbonyl electrophilicity caused by electronegative substituents.

Using the Passerini reaction, a multicomponent approach was developed leading to photolabile caged neurotransmitter, *7*-(*N*,*N*-diethylamino)-4-(hydroxymethyl) coumarin (DECM) caged gamma-aminobutyric acid. Another caged neurotransmitter, DECM caged carbamoylcholine chloride, was synthesized in a highly convergent one-pot process.

BIOGRAPHICAL SKETCH

Lijun Fan was born on February 27, 1979 in Tangshan, Hebei, China. While he had always had his heart in science, it was not until his junior year at Tangshan First High School that he was formally introduced to chemistry by Mr. Zhongmin Jin. After graduating with honors, the author attended Tsinghua University in Beijing, China. During his undergraduate studies, Lijun conducted research in organic synthesis in the laboratory of Professor Hong Tang. After graduating from Tsinghua with his B.S. in Chemistry in July 2001, the author traveled to the U.S where he entered the graduate program in chemistry at University of Missouri in the spring of 2002. In August 2004, after obtaining his M.S. degree under the guidance of Professor Shubhender Kapila, Lijun joined the graduate program in the Department of Chemistry and Chemical Biology at Cornell University. The author pursued a Ph.D. in organic chemistry under the guidance of Professor Bruce Ganem.

To my beloved parents, Zhimin Fan, Shumin Wang

and my wife Chih-Chin Liu

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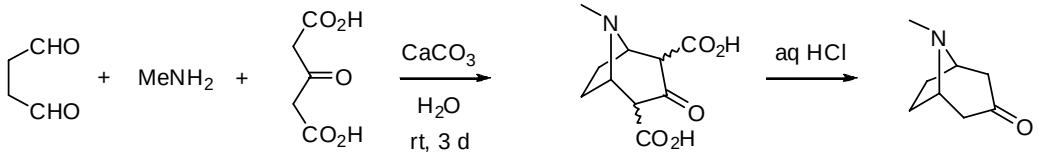
CHAPTER ONE

Development of Isonitrile-Based Multicomponent Reactions

1.1 Background

The ability to create complex molecules in a general and efficient manner has long challenged organic chemists. A good example of such an endeavor is the one-pot assembly of the bridged bicyclic alkaloid tropinone by Robert Robinson (Scheme 1.1).[1] This highly efficient synthesis was achieved by minimizing steps while maximizing structural and functional complexity.



17%

Scheme 1.1 Synthesis of Tropinone by Robinson

Because of increasing economic pressure and environmental concerns in the chemical and pharmaceutical industry, efficiency is now especially desirable in synthetic design. Among various ways to enhance synthetic efficiency, the used of multicomponent reactions constitutes a very attractive strategy.

A multicomponent reaction (MCR) is generally defined as a one-pot chemical process that affords one product from the combination of three or more reactants.[2] By forming multiple bonds in a single chemical operation, MCRs offer excellent synthetic efficiency. Other advantages over conventional bimolecular reactions include high selectivity, high atom-economy, convergence, and operational simplicity. Overall MCRs represent a big step towards Wender's concept of ideal synthesis, which "can be measured by parameters such as the step count, overall yield, selectivity, cost, scale, resource requirements, waste stream, development time, and execution time".[3]

MCRs are appealing in both target-oriented and diversity-oriented synthesis. Their convergence and high productivity can save operational time and cost in all

areas of applied synthesis. By virtue of their exploratory and complexity-generating power, MCRs are ideal tools with which large collections of structurally diverse compounds, also known as libraries, can be built. Screening such libraries has had enormous implications for the discovery of small molecules with desired properties, such as pharmaceutical reagents, synthetic compounds, biological probes and new catalysts.[4]

The first widely-recognized MCR was developed by Strecker in 1850.[5] The Strecker reaction enables the synthesis of α-amino acids via α-amino nitriles. Several other historically significant MCRs are listed in Table 1.1. Robinson's synthesis is, in fact, an ingenious application of the Mannich reaction.

With the introduction of high-throughput biological screening during 1990s, the demand for the number and quality of compounds used in drug discovery has increased dramatically. Driven by these challenges, MCR research evolved rapidly after 1995.[14] Many new and synthetically useful MCRs and variations have been developed to access hundreds of natural product-like or drug-like scaffolds. Furthermore, the combination of MCRs with other transformations has also flourished, providing even more structural diversity. Some significant achievements are listed in Table 1.2.

Table 1.1 Some Historically Significant MCRs

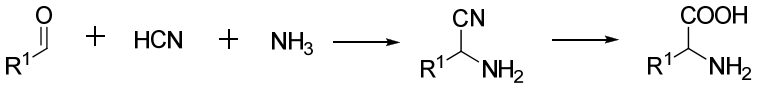
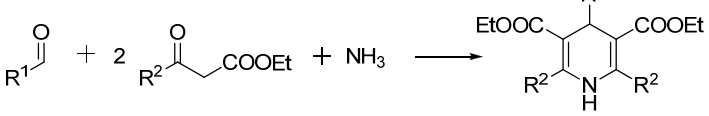
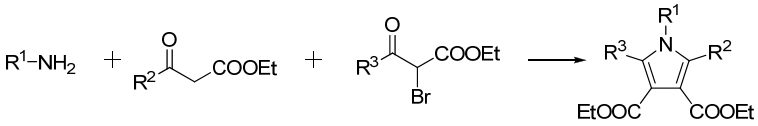
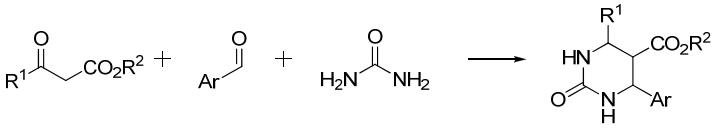
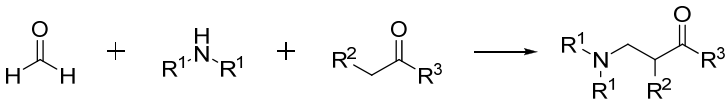
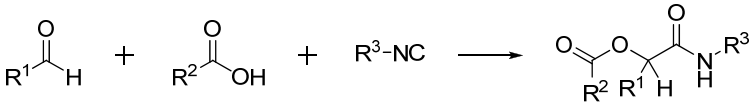
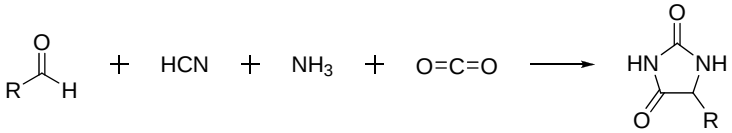
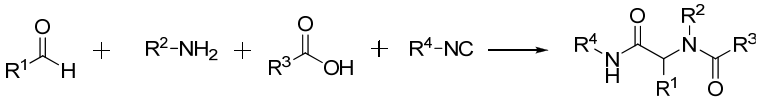
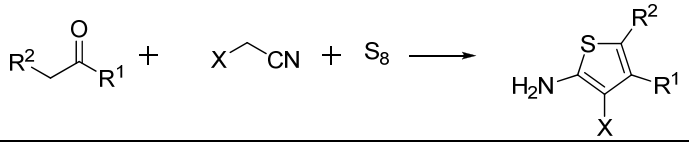
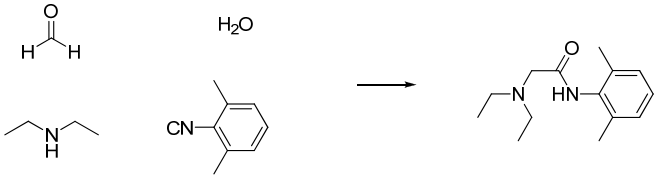
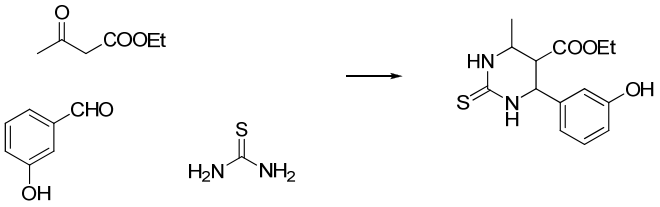
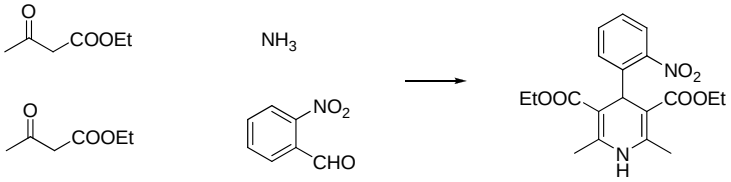
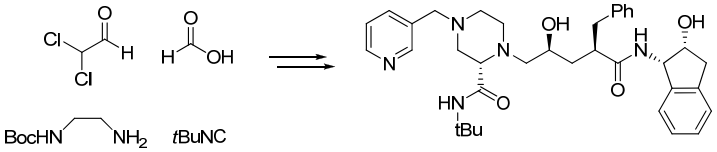
Name	Year	Example	
Strecker synthesis	1850		5
Hantzsch dihydro-pyridine synthesis	1882		6
Hantzsch pyrrole synthesis	1890		7
Biginelli reaction	1891		8
Mannich reaction	1912		9
Passerini reaction	1921		10
Bucherer-Bergs synthesis	1945		11
Ugi reaction	1959		12
Gewald reaction	1961		13

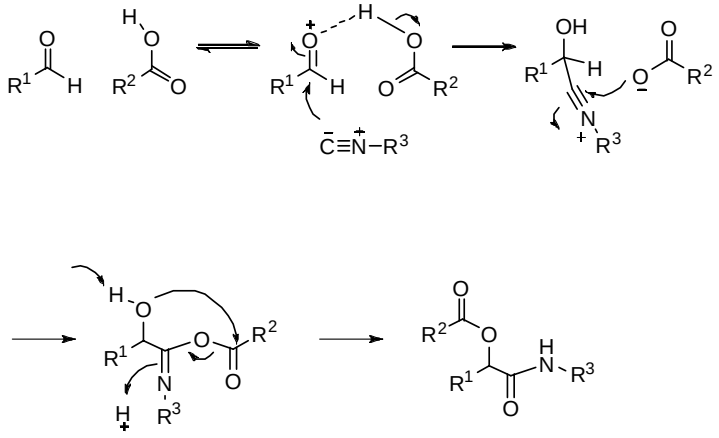
Table 1.2 Applications of MCRs

Name	Synthesis	Ref
Xylocain, by Ugi reaction		12
Monastrol by Biginelli reaction		15
Nifedipine by Hantsch reaction		6
Piperazine-2-carbox-amide, core structure of Crixivan, by Ugi-4CR.		16

1.2 Isonitrile-Based Multicomponent Reaction (IMCR) Chemistry

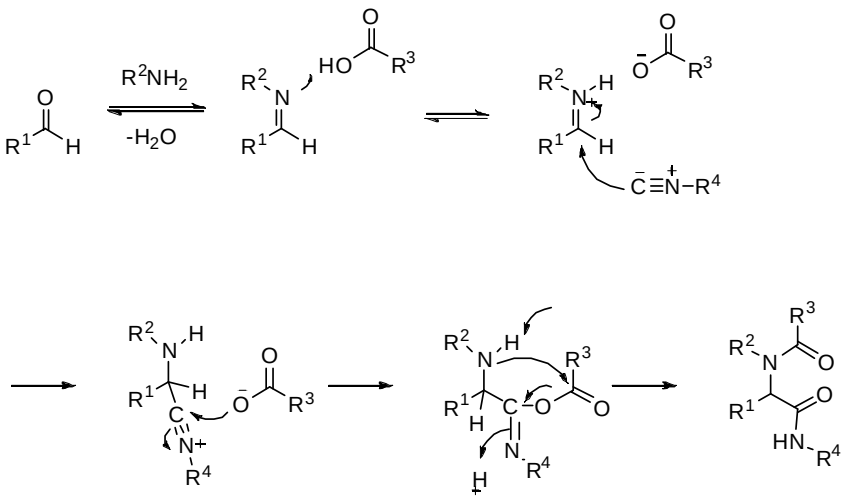
IMCRs constitute an extremely powerful subclass of MCRs. IMCRs rely on the unusual valence structure of isonitriles. The isonitrile functional group can be considered as a synthetic equivalent of vinylidene carbene, in which C^{II} is oxidized to C^{IV} in exothermic reactions.[17] The two most widely utilized MCRs, the Passerini and Ugi reactions, are both IMCRs.

The Passerini three-component reaction (Passerini 3CR) was originally described in 1921 by Mario Passerini.[10] The reaction enables the synthesis of α-acyloxy-carboxamides by combining a carboxylic acid, an aldehyde or ketone, and an isonitrile in one step. A plausible mechanism involves a sequence of 1) activation of the carbonyl group by partial hydrogen bonding, 2) α-addition of the isonitrile to the activated carbonyl compound and the carboxylate anion, 3) intramolecular Mumm rearrangement (Scheme 1.2).



Scheme 1.2 Mechanism of the Passerini 3CR

The Ugi four-component reaction (Ugi 4CR) converts an aldehyde or ketone, an amine, an acid and an isonitrile into an α-acylamino amide in one step, with good to excellent yields.[12] The mechanism involves imine formation, protonation of the imine followed by α-addition and Mumm rearrangement. As illustrated, the Ugi reaction has strong mechanistic similarities to the Passerini 3CR (Scheme 1.3).



Scheme 1.3 Mechanism of the Ugi 4CR

The Passerini and Ugi reactions are both robust reactions with excellent substrate scope and versatility. They are straightforward to perform and afford products in high yields with good purities. In fact, the large number of different molecular frameworks now available by MCR chemistry builds mostly on these two IMCRs and their combination with other reactions.[18]

1.3 Evolving Existing MCRs: Single Reactant Replacement

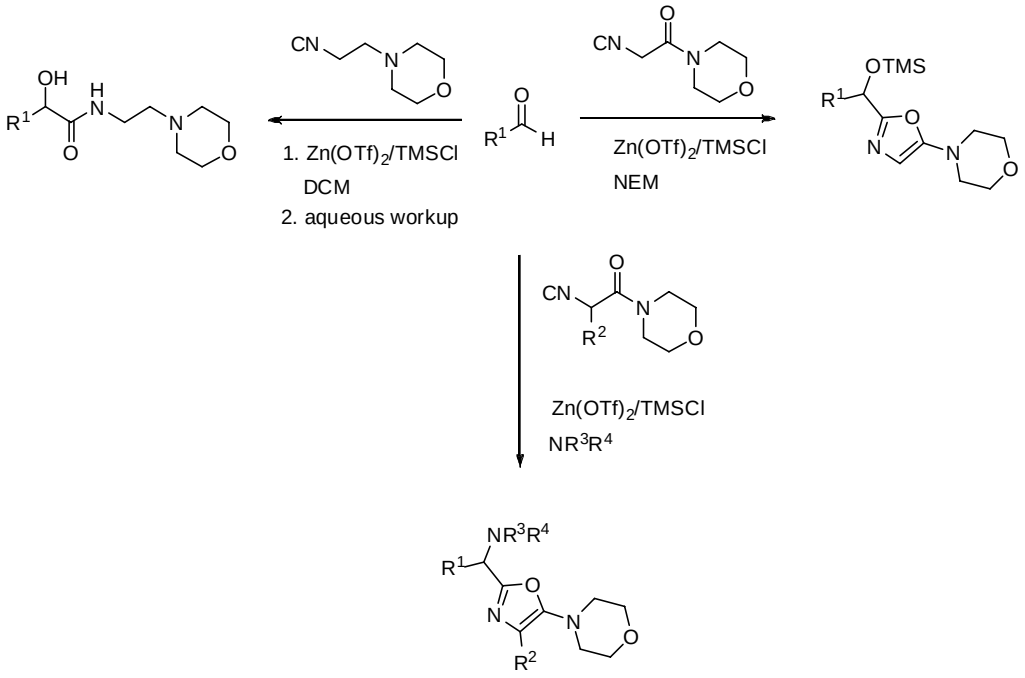
As powerful as MCRs are, their synthetic applications are still largely constrained by the number of available MCRs. The need to invent new MCRs, through which new scaffolds can be accessed, has stimulated research in new reaction discovery. Mainly four approaches have been described: random discovery, combinatorial chemistry, discovery by design, and union of MCRs.[19]

Our approach is a mechanism-based discovery strategy called single reactant replacement (SRR).[2] In SRR, one component of a known MCR is replaced with a component bearing an orthogonal reactivity element. The additional functionality undergoes subsequent reaction to redirect the reaction outcome, either spontaneously or upon treatment with additional reagents. Synthetic possibilities are hence increased

and ring systems may be prepared via intramolecular cyclization with appropriate substituents.

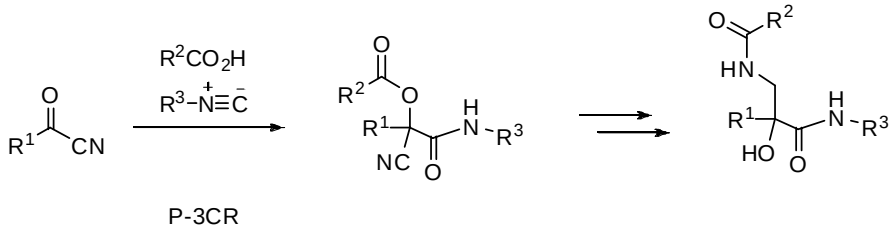
When evolving a known MCR using the SRR approach, three factors need to be considered. Firstly, starting materials should be readily available to insure a wide reaction scope and utility. Secondly, the key reactivity element in the multicomponent condensation step needs to be retained or enhanced. Thirdly, the expected product should resemble one or more bioactive structures.

Guided by SRR, our laboratory has made several discoveries over the years. Xia et al. investigated the effect of replacing the carboxylic acid component of the Passerini reaction with Lewis acids. [20] As a result, α-hydroxyamides and substituted oxazoles were synthesized by condensations of carbonyl compounds with appropriately substituted isonitriles capable of neighboring group donation (Scheme 1.4).



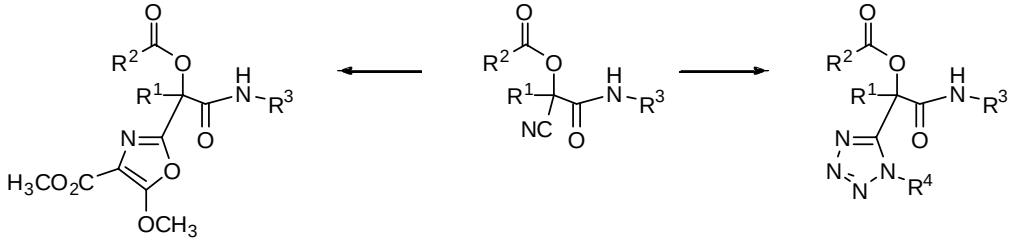
Scheme 1.4 Passerini Reaction with Lewis Acids

Oaksmith et al. discovered that by replacing the carbonyl compounds in the Passerini reaction with acylnitriles, β-aminoacid diamides were formed instead of the conventional α-acyloxyamides (Scheme 1.5).[21]



Scheme 1.5 Syntheses of β-Aminoacid Diamides via P-3CR

The application of acylnitriles in the Passerini reaction was further expanded by Clemençon et al. By combining the Passerini reaction with post-condensation dipolar cycloaddition reactions using either diazomalonic esters or alkyl azides, acyl nitriles were conveniently converted into 1,3-oxazoles or tetrazoles, respectively (Scheme 1.6).[22]



Scheme 1.6 Tandem MCR

1.4 IMCRs with α-Substituted Ketones

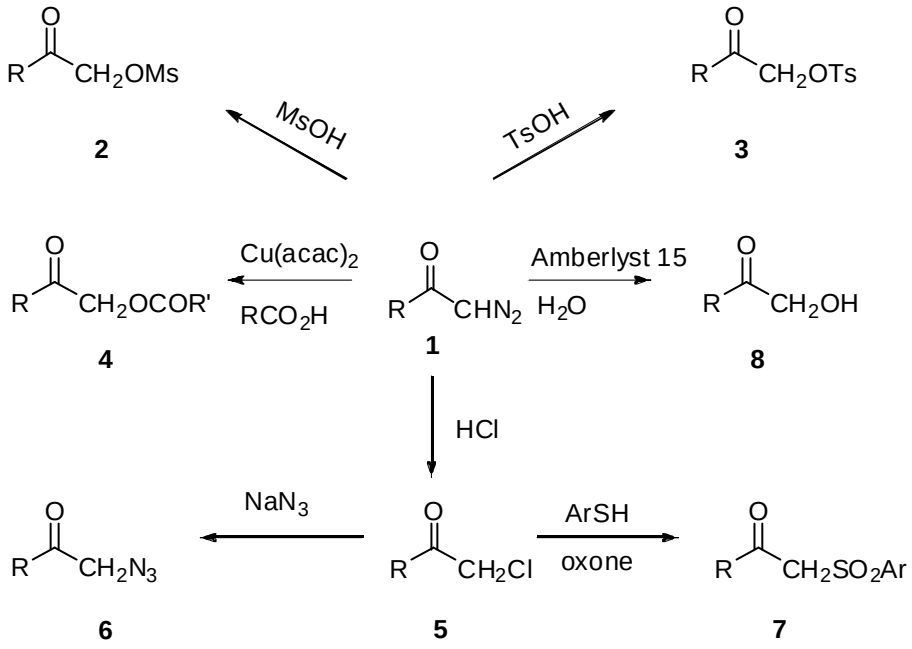
In continuing our group's efforts to evolve existing MCRs and to synthesize new molecular frameworks, we investigated α-substituted ketones as surrogates for simple carbonyl compounds in the Passerini and Ugi reactions.

Several reasons led us to study α-substituted ketones. Many α-substituted ketones are conveniently accessible from the corresponding acid chlorides. Moreover,

the Passerini and Ugi reactions with regular ketones are often sluggish because of the lack of reactivity at the carbonyl group. By adding an electron-withdrawing substituent at the α-position, the reactivity of the α-substituted ketone to nucleophilic addition is expected to increase. Finally, biologically important molecular scaffolds, including heterocycles, might be assembled.

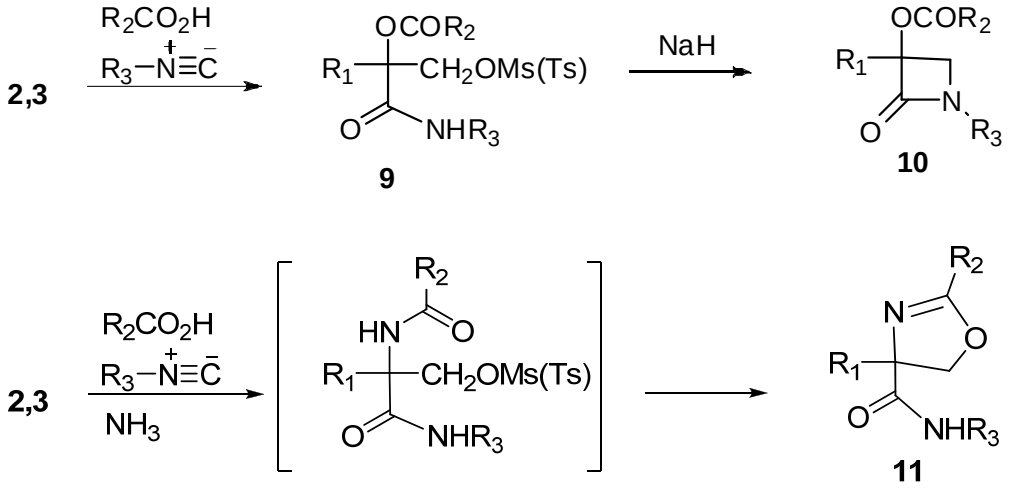
A comprehensive literature review showed that prior to our own study, there were few reports of Passerini of Ugi condensations on α-substituted ketones. The only example found was Sebti's use of α-chloroketones in a Passerini condensation to prepare chloro-substituted acyloxyamides, which were then transformed into acyoxyl-β-lactams when treated with sodium hydride.[23]

Several reactive α-substituents were of potential interest, including sulfonyloxy, acyloxy, azido, halo, hydroxyl and sulfonyl. In most cases, the starting material for α-substituted ketones was the corresponding α-diazoketone, which was available by reaction of the cognate acid chloride with diazomethane (Scheme 1.7).



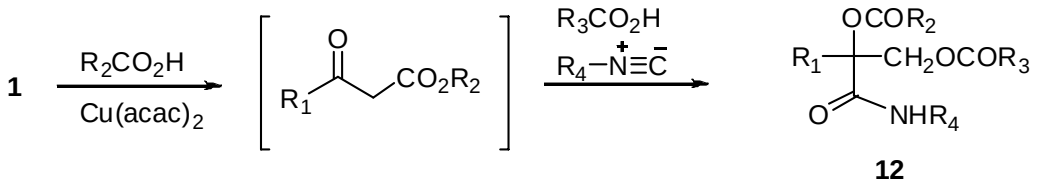
Scheme 1.7 Preparation of α-Substituted Ketones

Interestingly, α-diazoketones were found to be resistant to Passerini and Ugi conditions. The lack of reactivity was likely due to the resonance stabilization of the carbonyl group by the diazo group. Mesyloxy and tosyloxyketones **2** and **3,** respectively, proved to be excellent carbonyl components in the Passerini and Ugi reactions. As described in Chapter 4, the expected products **9** were formed in the Passerini reaction of **2** and **3**. Compound **9** was further converted to substituted β-lactams **10** upon treatment with NaH. In Chapter 2, substituted 2-oxazolines **11** were prepared in an efficient and general one-pot, four-component condensation in the Ugi reaction with ammonia (Scheme 1.8).[2, 23]



Scheme 1.8 Preparation of β-Lactams **10** and Oxazoline **11**

Chapter 3 reports the study of the reactivity of diazocarbonyls to carboxylic acids using transition metal catalysis. A one-pot, four-component condensation was achieved to furnish substituted di-*O*-acylglyceramides **12** from α-diazoketones (Scheme 1.9).[24]



Scheme 1.9 Preparation of Substituted Di-*O*-acylglyceramides **12**

The relative rates of reaction of various α-substituted ketones were studied in a representative Passerini condensation with acetic acid and t-butyl isonitrile under neat conditions at rt. (Chapter 4) The kinetic data were consistent with the expected enhancement of carbonyl electrophilicity caused by eletronegative substituents. The rate differences suggest of that chemoselective Passerini reaction could be achieved with certain α-substituted ketones.

In conclusion, the chemistry and reactivity of a broad range of α-substituted ketones in the Passerini and Ugi reactions were studied. The utility of these two powerful name reactions was significantly enhanced, and new dimensions were added to the chemical space accessible by these reactions. As new reactions and methodologies continue to emerge, the impact of MCRs on synthetic chemistry is expected to grow in the future.

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CHAPTER TWO

Bioactive 2-Oxazolines: A New Approach via One-Pot, Four-Component Reaction

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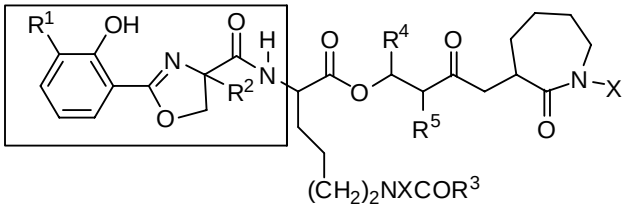
2.1 Introduction

Oxazolines are widely used in polymer chemistry as synthetic reagents and most recently as ligands in asymmetric synthesis.[1] Alkyl- and aryl-substituted 2-oxazolines are also present in marine natural products[2] and are important pharmacophores in numerous bioactive natural products that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties.

Some representative examples (Figure 2.1) include the cytotoxic agent brasilibactin **1**,[3] a family of five antitumor substances represented by B32030A **2** and B32030B **3**,[4] and the recently discovered T-cell antigen didehydroxymycobactin **3**, a complex lipopeptide related to the mycobactin family of mammalian siderophores that utilize the 2-hydroxyphenyloxazoline carboxamide substructure (box) to sequester iron in macrophages.[5]



1,X=OH; R^1-R^3=H; R^4,R^5=CH_3 *brasilibactin A*

2,X=OH; R^2,R^4, R^5=H; R^4=CH_3; R^3=*n*-$C_{12}H_{25}$
R1=H (*BE-32030A*) or R1=OH (*BE-32030D*)

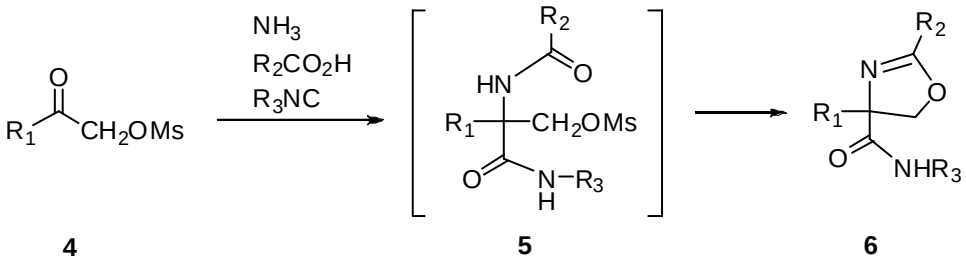
3,X=H; R^1,R^5=H; R^4=CH_3; R^3=*cis*-CH=CH-$(CH_2)_{16}CH_3$
didehydroxymycobaction

Figure 2.1 Substituted 2-Oxazolines in Bioactive Natural Products.

We have been interested in developing convergent synthetic routes to such complex oxazolines utilizing a multicomponent reaction to assemble the key heterocyclic pharmacophore in a single flask. Here, we report a powerful and versatile 4-component condensation that efficiently produces 2-substituted oxazoline-4-carboxamides and their congeners as highlighted in **1**-**3** in good yields.

The approach we envisioned was based on the known biosynthesis of many peptide-derived oxazolines, which usually involves cyclization of *N*-acyl serine residues. We initially considered an Ugi reaction using α-diazoketones (readily prepared from acid chlorides using CH_2N_2) in place of simple aldehydes or ketones. However, mixtures of α-diazoketones, amines, isonitriles, and carboxylic acids proved unreactive, even when heated to 60-70 °C.

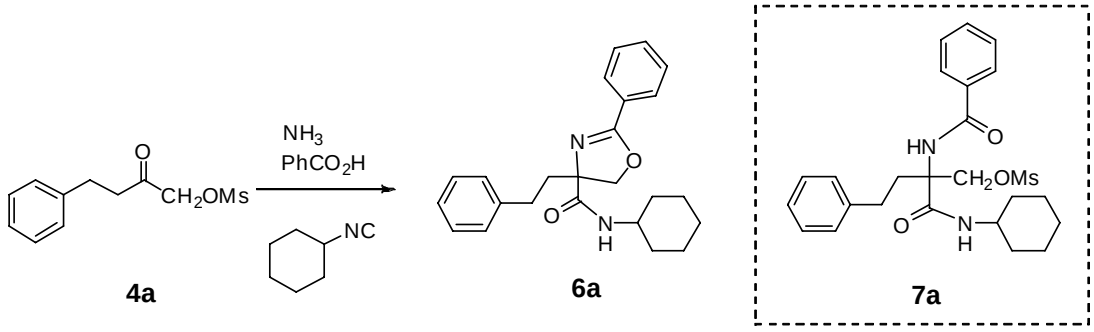
We therefore investigated Ugi condensations of the corresponding (and much more electrophilic) α-ketomesylates **4** (Scheme 2.1), which are readily available by the known insertion reaction[6] of diazoketones with CH_3SO_3H. Our expectation was that if imine formation at the carbonyl group in **4** using ammonia were faster than displacement of the mesylate, then the intermediate diamide **5** might spontaneously cyclize in situ to the desired oxazoline **6**.



Scheme 2.1 Proposed MCR Approach to Substituted 2-Oxazolines

2.2 Result and Discussion

Using the β-ketomesylate **4a** (Scheme 2.2) as a test case, a solution of **4a** in CH_3OH was stirred with NH_3 and benzoic acid (1 equiv each) for 30 min at 0 °C. After adding cyclohexylisonitrile (1.1 equiv) then stirring at rt for 24 h, solvent evaporation led directly to roughly equal quantities of the target oxazoline **6a** together with the corresponding three-component Passerini product **7a**. Increasing the quantities of ammonia and benzoic acid slightly improved the yield of **6a** but did not suppress formation of **7a**. A more dramatic improvement was achieved by replacing methanol as solvent with 2,2,2-trifluoroethanol, which has been shown to improve Ugi reactions involving ammonia.[7] Under optimal conditions (4 equiv each of NH_3, $PhCO_2H$), **6a** was obtained in 61% yield (mp 89 °C) accompanied by ca. 5% of **7a**. Interestingly, no products derived from simple nucleophilic substitution of the mesylate group in **4a** were observed.



Scheme 2.2 One-Pot Synthesis of 2-Oxazolines

The X-ray crystal structure of **6a** confirmed the presence of the 2,4,4-trisubstituted oxazoline ring. (Figure 2.2)

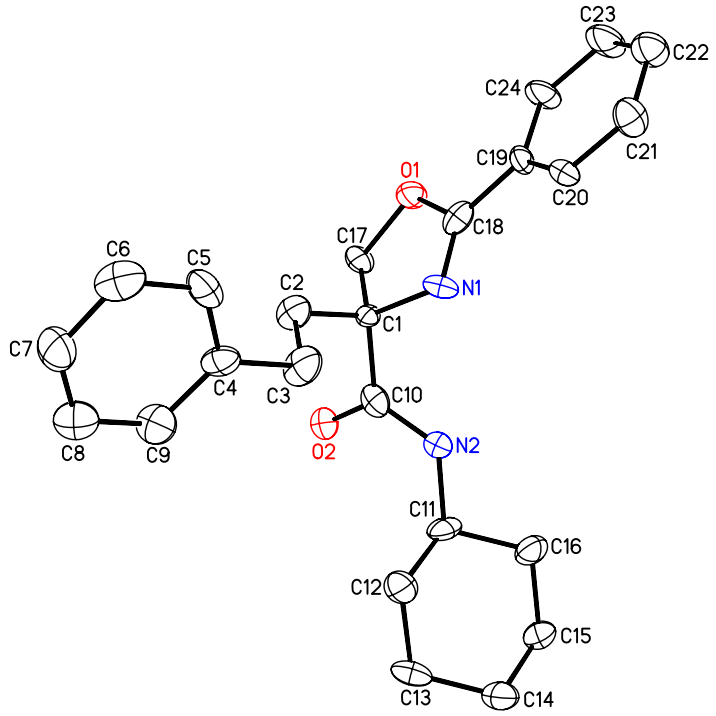


Figure 2.2 ORTEP Diagram of the X-ray Crystal Structure of Oxazoline **6a**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (deg): N(1)-C(18)) 1.270(3), O(1)-C(18)) 1.369(3), C(1)-N(1)) 1.474(3), O(1)-C(17)) 1.444(3);N(1)-C(1)-C(17)) 104.45(18), N(1)-C(18)-O(1)) 118.5(2), C(18)-O(1)-C(17)) 105.55(18), C(10)-C(1)-C(17)) 110.7(2), C(10)-C(1)-C(2)) 106.70(19).

Several examples of trisubstituted 2-oxazolines prepared by this four-component condensation illustrate the scope and generality of the method (Table 2.1). Precondensing the carboxylic acid ammonium salt (4 equiv) and the ketomesylate in CF_3CH_2OH for 30 min at 0 °C is sufficient to minimize the formation of Passerini products like **7**.

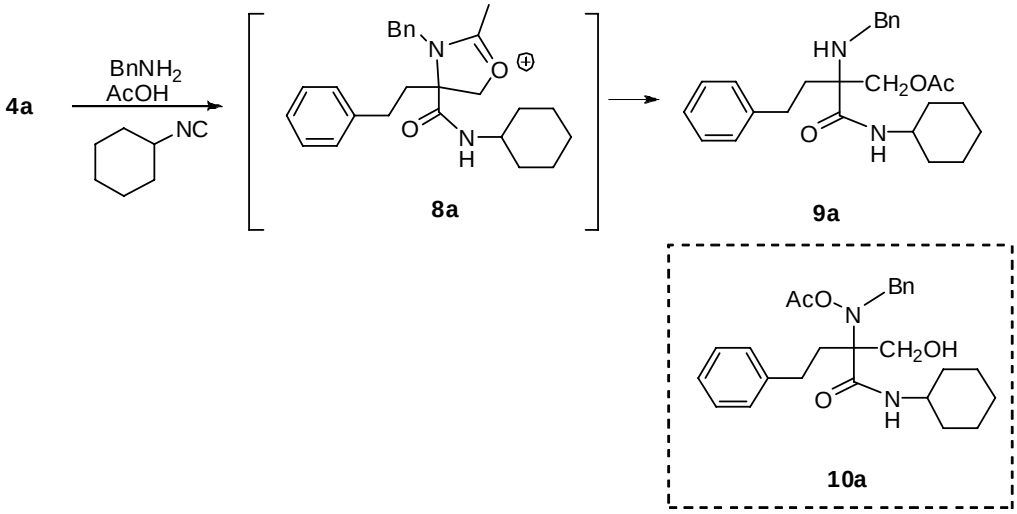
Table 2.1 Synthesis of 2-Oxazolines **6** from Ketomesylates **4**

ketomesylate	R^2CO_2H	R^3NC	Product
4a-e	R^2 =	R^3 =	(% yield)
4a, R= $Ph(CH_2)_2$	C_6H_5	cyclohexyl	**6a**(61)
	CH_3	cyclohexyl	**6b** (71)
	CH_3	*tert*-butyl	**6c** (73)
	Boc-(*S*)-Phe	cyclohexyl	**6d** (64)[a]
4b, R = *n*-C_7H_{15}[b]	*i*-C_3H_7	CH_2CO_2Et	**6e** (60)
	CH_3	*tert*-butyl	**6f** (80)
	Cbz-Gly	*tert*-butyl	**6g** (38)
4c, R = cyclohexyl	CH_3	CH_2CO_2Et	**6h** (63)
	i-C_3H_7	*tert*-butyl	**6i** (60)
4d, R = Ph[b]	CH_3	*tert*-butyl	**6j** (63)
4e, R = CH_3[c]	CH_3	*tert*-butyl	**6k** (60)
	C_6H_5	CH_2CO_2Et	**6l** (68)
	o-$(OH)C_6H_4$	*tert*-butyl	**6m** (58)[d]
	o-$(OH)C_6H_4$	CH_2CO_2Et	**6n** (63)[d,e]

[a] Obtained as a mixture of diastereomers. [b] Cho, B. T.; Yang, W. K.; Choi, O. K. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1204. [c] Lodaya, J. S.; Koser, G. *J. Org. Chem.* **1988**, *53*, 210. [d] CH_3OH was used as solvent in this reaction. [e] 2 equiv of isonitrile was used in this reaction.

As the examples in Table 2.1 indicate, a broad range of carboxylic acids and isonitriles (including examples of both compound families derived from naturally occurring α-amino acids) underwent smooth reaction with various ketomesylates and ammonia to form the desired 2-oxazolines. Even resonance-stabilized ketomesylates such as $PhCOCH_2OMs$ **4d** were reactive enough to form the desired oxazoline carboxamides, e.g., **6j**, in good yield.

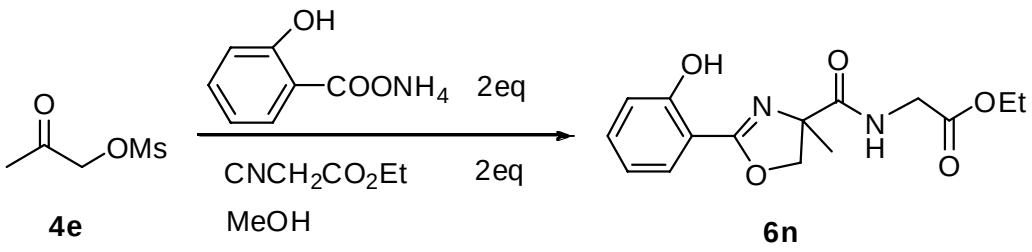
When ammonia was replaced with a primary amine, such as benzyl or allylamine, the multicomponent reaction took a different course, affording aminoesters like **9a** (Scheme 2.3) as the exclusive product from ketomesylate **4a**. The structure of **9a**, which was also confirmed by single-crystal X-ray diffraction analysis, most likely arose via hydrolysis of an intermediate oxazolinium ion like **8a**. Interestingly, none of the isomeric amido alcohol **10a** was detected.



Scheme 2.3 MCR Route to Aminoester **9a** from **4a**

The new oxazoline synthesis could also be applied (Scheme 2.4) to a one-pot assembly of the 2-hydroxyphenyl-4-methyloxazoline-4-carboxamide substructure found in natural products like **1**-**3**. Initial attempts using salicylic acid as the

carboxylic acid component failed in trifluoroethanol because of the insolubility of ammonium salicylate. However, the problem was overcome by switching to methanol as solvent. Gratifyingly, the desired oxazoline **6n** was produced in 63% yield. Furthermore, no phenol protecting group was required, in contrast to earlier total synthesis efforts in the mycobactin series.[8]



Scheme 2.4 Assembly of 2-Oxazoline Substructures in **1-3**

2.3 Conclusion

In summary, we have developed an efficient four component reaction that affords 2-substituted oxazoline-4-carboxamides in a one-pot process from readily available starting materials. With their widespread occurrence in bioactive natural products, such functionalized oxazolines may be considered privileged structures, i.e., molecular frameworks exhibiting medicinally useful binding properties. The multicomponent synthesis reported here rapidly assembles promising lead compounds containing this heterocyclic system for use in drug discovery endeavors.

2.4 Experimental Procedures

Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR were taken on a Varian Mercury-300, Varian Inova-400 or Varian Inova-500 spectrometer as indicated using $CDCl_3$ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and were referenced to TMS (0.00 ppm for ^{1}H NMR) and $CDCl_3$ (77.23 ppm for ^{13}C

NMR). IR spectra were obtained on a Mattson Instruments Galaxy Series FT-IR spectrometer and were recorded in wavenumbers (cm^{-1}). Chemicals were obtained from Aldrich, Fluka, Fisher, Lancaster, Mallinckrodt, or Novabiochem and used as received unless specified. Ether was distilled from sodium/benzophenone. Methanol and 2,2,2-trifluoroethanol was distilled from CaH_2. In reactions leading to diastereomers, spectroscopic data were reported for mixtures, unless specified otherwise.

Synthesis of ketomesylates 4a and 4c from diazoketones and methanesulfonic acid.

*1-Mesyloxy-4-phenyl-2-butanone **4a**:* To methanesulfonic acid (3.85 mmol) in anhydrous ether (10 mL) at 0 °C, was slowly added a solution of 1-diazo-4-phenyl-2-butanone (3.5 mmol) in anhydrous ether (5 mL) by syringe over a 10 min period. The reaction mixture was stirred for 10 min at 0 °C, then 10 min at rt. Water (10 mL) was then added with stirring for 30 min at rt. After separating the layers, the aqueous phase was extracted with ether (3 x 10 mL) and the combined ether layers were washed with H_2O (3 x 10 mL) and saturated NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.2), to afford the desired product as a white solid (0.7 g, 83%): mp 56-57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.32 (m, 5H), 4.72 (s, 2 H), 3.16 (s, 3 H), 2.95 (t, 2 H, *J*= 7.4 Hz), 2.80 (t, 2 H, *J*= 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.31, 140.18, 128.88, 128.49, 126.70, 71.80, 40.42, 38.96, 29.26; IR (CH_2Cl_2) 3055(s), 1742(s), 1360(s), 1179(s); CIMS (methane) *m/z* 243(M+H), 219, 147, 129.

*(Mesyloxyacetyl)cyclohexane **4c**:* The crude product was purified by silica gel flash column chromatography (3:7 hexanes:ethyl acetate, Rf=0.3), to afford the desired product as white solid (97% yield): mp 71°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 2

H), 3.21 (s, 3 H), 2.44 (m, 1 H), 1.80 (t, 4 H, J=12.1 Hz), 1.70 (br d, 1 H, J=10.5 Hz), 1.2-1.4 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.99, 71.11, 47.53, 39.59, 28.57, 26.06, 25.86; IR (CH_2Cl_2) 3055(s), 2938(s), 1732(s), 1356(s), 1177(s); CIMS (methane) *m/z* 221(M+H), 125, 107.

Representative procedure for the synthesis of 2-substituted oxazoline-4-carboxamides 6a-n.

*Compound **6a**:* To a solution of **4a** (0.2 mmol) in anhydrous 2,2,2-trifluoroethanol (0.5 mL) at 0 ^{o}C was added ammonium benzoate (0.8 mmol). The reaction mixture was stirred for 30 min at 0 °C, then cyclohexyl isocyanide (0.22 mmol) was added via syringe with stirring. The reaction mixture was warmed to rt and stirred for 18 h. The solvent was evaporated under reduced pressure to give an oil. The crude product obtained was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.5) to afford **6a** as a white solid (48 mg, 61%): mp 89 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (m, 2 H), 7.14-7.55 (m, 8 H), 6.72 (d, 1 H, *J*= 8.4 Hz), 4.64 (d, 1 H, *J*= 9.1 Hz), 4.34 (d, 1 H, *J*= 9.1 Hz), 3.77 (m, 1 H), 2.81 (td, 1 H, *J*= 13.2, 4.6 Hz), 2.59 (td, 1 H, *J*= 13.2, 4.6 Hz), 2.30 (td, 1 H, *J*= 13.1, 5.0 Hz), 1.96-2.06 (m, 2 H), 1.83-1.86 (m, 1 H)1.58-1.75 (m, 3 H), 1.11-1.44 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.97, 164.35, 141.39, 131.77, 128.40, 128.33, 128.29, 128.25, 127.21, 125.77, 77.58, 75.13, 47.75, 41.41, 33.08, 32.78, 30.02, 25.38, 24.69; IR (CH_2Cl_2) 3387(s), 2934(s), 1666(s), 1647(s), 1516(s), 1452(s); CIMS (methane) *m/z* 377 (M+H), 250, 179.

Also obtained was a small quantity of the corresponding Passerini reaction product **7a** as a white solid (5% yield), which was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.2) and shown to be identical to an authentic sample prepared by the reaction of **4a** with benzoic acid and cyclohexyl isocyanide: mp 105-110 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.94(m, 10 H), 6.45 (d,

1 H, *J*= 8.6 Hz), 5.16 (d, 1 H, *J*= 10.0 Hz), 4.71 (d, 1 H, *J*= 8.9 Hz), 3.89 (m, 1 H), 2.94 (s, 3H), 2.56-2.70 (m, 3 H), 2.40-2.45 (m, 1 H), 1.96-2.06 (m, 2 H), 1.72-1.77 (m, 2 H), 1.62-1.66 (m, 1 H), 1.38-1.46 (m, 2 H), 1.22-1.29 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.79, 164.73, 140.19, 133.96, 129.82, 129.64, 128.98, 128.67, 128.53, 126.44, 85.47, 70.01, 48.78, 37.33, 33.60, 33.19, 32.99, 29.62, 25.57, 24.83, 24.77; IR (CH_2Cl_2) 3443(m), 3055(s), 2937(m), 1730(s), 1680(s), 1520(s), 1364(s); CIMS (methane) *m/z* 474 (M+H), 378, 256.

*Compound **6b**:* The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.3) to afford **6b** as a white solid (71% yield): mp 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.28 (m, 5 H), 6.58 (d, 1 H, *J*= 8.1 Hz), 4.46 (d, 1 H, *J*= 9.3 Hz), 4.26 (d, 1 H, *J*= 9.3 Hz), 3.77 (m, 1 H), 2.75 (td, 1 H, *J*= 13.1, 4.8 Hz), 2.53 (td, 1 H, *J*= 12.8, 4.9 Hz), 2.20 (td, 1 H, *J*= 13.1, 4.8 Hz), 2.05 (s, 3 H), 1.90 (m, 3 H), 1.71 (m, 2 H), 1.60 (m, 1 H), 1.38 (m, 2 H), 1.22 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.20, 166.49, 141.58, 128.58, 128.56, 126.12, 77.59, 75.50, 48.11, 41.69, 33.36, 33.09, 30.32, 25.66, 25.03, 24.99, 14.43; IR (CH_2Cl_2) 3354(s), 2936(s), 1649(b, s), 1502(s); CIMS (methane) *m/z* 315 (M+H), 234, 206, 100.

*Compound **6c**:* The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.4) to afford **6c** as a clear oil (73% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.29 (m, 5 H), 6.52 (s, 1 H), 4.45 (d, 1 H, *J*= 9.2 Hz), 4.10 (d, 1 H, *J*= 9.2 Hz), 2.72 (td, 1 H, *J*= 13.4, 4.7 Hz), 2.51 (td, 1 H, *J*= 12.8, 4.7 Hz), 2.19 (td, 1 H, *J*= 13.1, 4.9 Hz), 2.05 (s, 3 H), 1.88 (td, 1 H, *J*= 13.1, 4.8 Hz), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.40, 166.29, 141.71, 128.60, 128.59, 126.12, 77.85, 75.47, 51.19, 41.78, 30.33, 28.95, 14.47; IR (CH_2Cl_2) 3381(s), 2968(s), 1672(s), 1518(b, s); CIMS (methane) *m/z* 289 (M+H), 233, 188.

*Compound **6d:*** (diastereomers) The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.4) to afford **6d** as a clear oil (64% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-7.30 (m, 10 H), 6.45 (d, 0.5 H, *J*= 8.1 Hz), 6.31 (d, 0.5 H, *J*= 8.1 Hz), 5.02 (d, 1 H, *J*= 7.5 Hz), 4.70 (t, 1 H, *J*= 5.8 Hz), 4.51 (d, 0.6 H, *J*= 9.0 Hz), 4.45(d, 0.4 H, *J*= 8.8 Hz), 4.18 (d, 0.4 H, *J*= 8.8 Hz), 4.16 (d, 0.6 H, *J*= 9.0 Hz), 3.70 (m, 1 H), 3.10 (m, 2 H), 2.55 (m, 1 H), 2.39 (m, 1 H), 2.15 (m, 1 H), 1.59-1.90 (m, 6 H), 1.47 (s, 9 H), 1.03-1.47(m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.61, 167.39, 155.21, 141.53, 135.92, 129.71, 129.62, 128.73, 128.61, 128.55, 128.52, 128.50, 127.32, 127.22, 126.08, 80.29, 77.36, 77.34, 76.43, 76.05, 50.34, 50.07, 48.24, 48.14, 41.40, 38.71, 38.33, 33.30, 33.23, 32.99, 30.29, 30.13, 28.58, 28.55, 25.67, 25.08, 25.05; IR (CH_2Cl_2) 3431(w), 3055(s), 2935(s), 1712(s), 1664(s), 1520(s); CIMS (methane) *m/z* 520 (M+H), 492, 464, 420.

*Compound **6e*:** The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.5) to afford **6e** as a clear oil (60% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, 1 H, *J*= 5.5 Hz), 4.38 (d, 1 H, *J*= 9.6 Hz), 4.20 (dd, 2 H, *J*= 14.7, 7.2 Hz), 4.10 (d, 1 H, *J*= 9.3 Hz), 4.02 (ddd, 2 H, *J*= 19.1, 13.4, 6.1 Hz), 3.60 (m, 1 H), 1.80 (m, 1 H), 1.67 (m, 2 H), 1.19-1.30 (m, 19H), 0.87 (t, 3 H, *J*= 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.46, 173.55, 169.71, 77.41, 74.71, 61.62, 41.16, 39.16, 32.00, 29.82, 29.34, 28.56, 23.50, 22.83, 20.03, 19.91, 14.35, 14.29; IR (CH_2Cl_2) 3398(m), 3055(s), 2931(s), 1745(s), 1674(s), 1520(s); CIMS (methane) *m/z* 341 (M+H), 210.

*Compound **6f:*** The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.5) to afford **6f** as a clear oil (80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1 H), 4.40 (d, 1 H, *J*= 9.3 Hz), 4.05 (d, 1 H, *J*= 9.3 Hz), 2.02 (s, 3 H), 1.79 (m, 1 H), 1.60 (m, 1 H), 1.35 (s, 9 H), 1.20-2.30 (m, 10 H), 0.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.85, 165.86, 77.99, 75.46,

51.06, 39.86, 31.96, 29.84, 29.35, 28.94, 23.80, 22.81, 14.41, 14.28; IR (CH_2Cl_2) 3381(m), 2930(s), 1670(s), 1520(s), 1265(s); CIMS (methane) *m/z* 283 (M+H), 227, 182.

*Compound **6g***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.3) to afford **6g** as a clear oil (38% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.38 (m, 5 H), 6.35 (s, 1 H), 5.35 (s, 1 H), 5.15 (s, 2 H), 4.49 (d, 1 H, *J*= 9.0 Hz), 4.12 (d, 1 H, *J*= 9.0 Hz), 4.05 (m, 2 H), 1.81 (m, 1 H), 1.60 (m, 1 H), 1.35 (s, 9 H), 1.25-1.30 (m, 10 H), 0.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.22, 165.06, 156.29, 136.38, 128.81, 128.53, 128.36, 77.45, 76.38, 67.34, 51.19, 39.62, 38.82, 31.97, 29.79, 29.35, 28.89, 23.77, 22.83, 14.29; IR (CH_2Cl_2) 3441(m), 3055(s), 2930(s), 1726(s), 1670(s), 1522(s), 1265(s); CIMS (methane) *m/z* 432(M+H), 376, 324.

*Compound **6h***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.1) to afford **6h** as a white solid (63% yield): mp 86-89 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1 H), 4.34 (d, 1 H, *J*= 9.1 Hz), 4.24 (d, 1 H, *J*= 9.1 Hz), 4.22 (dd, 2 H, *J*= 6.9, 3.3 Hz), 4.03 (ddd, 2 H, J= 18.1, 9.8, 5.9 Hz), 2.02 (s, 3 H), 1.61-1.79 (m, 6 H), 1.09-1.35 (m, 7 H), 0.89 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.00, 169.74, 166.12, 81.14, 73.50, 61.63, 45.09, 41.11, 27.48, 26.48, 26.40, 26.37, 26.22, 14.35, 14.23; IR (CH_2Cl_2) 3400(m), 3055(s), 2933(s), 1745(s), 1670(s), 1520(s); CIMS (methane) *m/z* 297 (M+H), 251, 166.

*Compound **6i***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.5) to afford **6i** as a clear oil (60% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1 H), 4.29 (d, 1 H, *J*= 9.1 Hz), 4.18 (d, 1 H, *J*= 9.1 Hz), 2.61 (m, 1 H), 1.59-1.74 (m, 7 H), 1.34 (s, 9 H), 1.05-1.24(m, 9 H), 0.89 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.04, 172.72, 80.48, 73.45, 50.95, 44.91, 28.97, 28.59, 27.42, 26.52, 26.51, 26.47, 26.13, 20.13, 20.02; IR (CH_2Cl_2)

3377(s), 2931(s), 1732 (w), 1664(s), 1518(s), 1454(s); CIMS (methane) *m/z* 295 (M+H), 239, 194.

*Compound **6j**:* The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.35) to afford **6j** as a clear oil (63% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.44 (m, 5 H), 6.49 (s, 1 H), 5.01 (d, 1 H, *J*= 9.0 Hz), 4.28 (d, 1 H, *J*= 9.0 Hz), 2.11 (s, 3 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.23, 166.11, 143.08, 128.73, 127.76, 125.47, 80.48, 76.97, 51.22, 28.81, 14.42; IR (CH_2Cl_2) 3381(m), 3055(s), 2985(s), 1676(s, br), 1518(s); CIMS (methane) *m/z* 261 (M+H), 205, 161.

*Compound **6k**:* The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.1) to afford **6k** as a clear oil (70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 1 H), 4.45 (d, 1 H, *J*= 9.1 Hz), 4.02 (d, 1 H, *J*= 9.1 Hz), 2.01 (s, 3 H), 1.43 (s, 3 H), 1.09-1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90, 165.69, 76.41, 74.34, 50.64, 28.57, 26.48, 14.13; IR (CH_2Cl_2) 3383(s), 2976(s), 1745(w), 1668(s), 1518(s), 1267(s); CIMS (methane) *m/z* 199 (M+H), 171, 143.

*Compound **6l***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.1) to afford **6l** as a clear oil (82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-8.12 (m, 2 H), 7.41-7.54 (m, 3 H), 7.36 (s, 1 H), 4.70 (d, 1 H, *J*= 9.1 Hz), 4.27 (d, 1 H, *J*= 9.1 Hz), 4.21 (dd, 2 H, *J*= 6.9, 4.2 Hz), 4.05 (ddd, 2 H, *J*= 14.1, 10.0, 5.6 Hz), 1.62 (s, 3 H), 1.26 (t, 3 H, *J*= 7.16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.44, 169.67, 165.09, 132.18, 130.28, 128.71, 128.65, 128.60, 127.25, 76.68, 74.73, 61.66, 41.29, 26.56, 14.30; IR (CH_2Cl_2) 3400(m), 3055(s), 2986(s), 1745(s), 1680(s), 1520(s), 1265(s); CIMS (methane) *m/z* 291 (M+H), 245, 160.

*Compound **6m***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.5) to afford **6m** as a white solid (58% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ11.44 (s, 1 H), 6.90-7.71 (m, 4 H), 6.24 (s, 1 H), 4.65 (d, 1 H, *J*= 8.8 Hz), 4.22 (d, 1 H, *J*= 8.8 Hz), 1.59 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.10, 166.24, 159.89, 134.38, 128.66, 119.39, 117.08, 110.48, 76.14, 74.61, 51.32, 28.83, 26.92; IR (CH_2Cl_2) 3408(m), 3055(s), 2982(s), 1672(s), 1639(s), 1514(s); CIMS (methane) *m/z* 277 (M+H), 249, 176.

*Compound **6n***: The crude product was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.2) to afford **6n** as a clear oil (63% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ11.37 (s, 1 H), 6.89-7.69 (m, 5 H), 4.70 (d, 1 H, *J*= 8.8 Hz), 4.26 (d, 1 H, *J*= 8.8 Hz), 4.21(dd, 2 H, *J*= 14.4, 7.5 Hz),4.03 (ddd, 2 H, *J*= 13.4, 18.4, 5.7 Hz), 1.66 (s, 3 H), 1.27 (t, 3 H, *J*= 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.32, 169.44, 166.78, 159.96, 134.49, 128.69, 119.37, 117.15, 110.29, 76.04, 74.35, 61.84, 41.35, 26.63, 14.30; IR (CH_2Cl_2) 3423(m), 3055(s, br), 2985(s, br), 1745(s), 1680(s), 1639(s), 1518(s); CIMS(methane) *m/z* 307 (M+H), 176, 86.

Four-component condensation of ketomesylates using a primary amine.

*Synthesis of aminoester **9a**:* To a solution of ketomesylate **4a** (0.2 mmol) in anhydrous 2,2,2-trifluoroethanol (0.5 mL) at 0 °C was added benzylamine (0.8 mmol) by syringe dropwise. The reaction mixture was stirred for 10 min at 0 °C, then acetic acid (0.4 mmol) and cyclohexyl isocyanide (0.22 mmol) were added via syringe with stirring. The reaction mixture was warmed to rt and stirred for 18 h. The solvent was evaporated *in vacuo* to give an oil, which was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, R_f= 0.3) to afford **9a** as a white solid (57 mg, 71%): mp 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.40 (m, 10 H), 4.45-4.53 (dd, 2 H, *J*= 18.6, 11.6 Hz), 3.83 (m, 1 H), 3.75 (d, 1 H, *J*= 12.4 Hz), 3.61 (d, 1 H, *J*= 12.4 Hz), 2.65 (m, 2 H), 2.07 (s, 3 H), 1.82-2.00 (m, 3 H), 1.60-1.73 (m, 4 H), 1.33-

1.44 (m, 2 H), 1.14-1.24 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.38, 170.72, 141.56, 139.80, 128.88, 128.65, 128.44, 128.21, 127.62, 126.23, 64.10, 63.97, 47.94, 47.12, 36.74, 33.45, 33.27, 30.11, 25.65, 24.96, 24.94, 21.08; IR (CH_2Cl_2) 3350(s), 2932(s), 1740(s), 1665(s), 1516(s), 1452(s), 1379(s); CIMS (methane) *m/z* 405 (M+H), 363, 296.

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CHAPTER THREE

Multicomponent Reaction Design: a One-pot Route to Substituted Di-*O*-acylglyceric Acid Amides from α-Diazoketones

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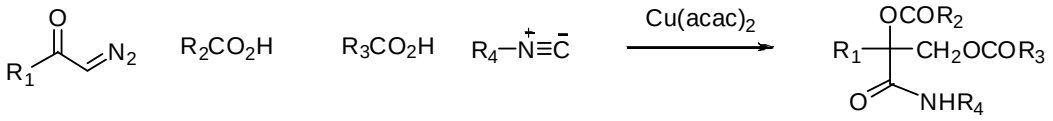
3.1 Introduction

Multicomponent reactions have attracted the attention and interest of synthetic chemists as efficient processes for the assembly of densely functionalized structures. MCRs are of special interest in making compounds that exhibit pharmacological activity.[1] As part of our laboratory's effort to expand the repertoire of useful MCRs, we have investigated the utility of functionalized carbonyl compounds such as acyl cyanides[2] and acyltetrazoles[3] in isonitrile-based multicomponent condensations, whose scope has traditionally been limited to simple aldehydes and ketones.[4] Here, we report a versatile, 4-component condensation of readily available α-diazoketones with (two) carboxylic acids and isonitriles to afford a new family of structurally diverse, substituted di-*O*-acylglyceramides **5** (Scheme 3.1).



1 **2** **3** **4** **5**

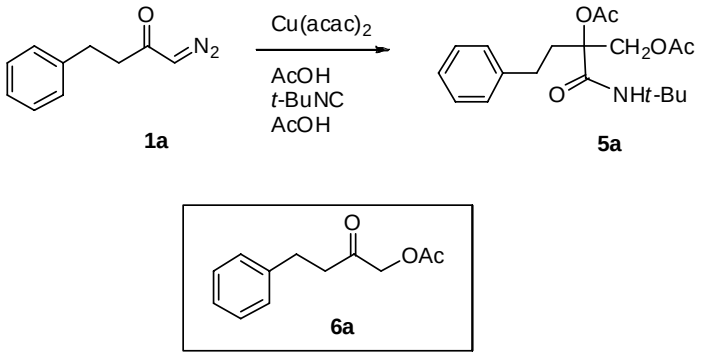
Scheme 3.1 Synthesis of Substituted Di-*O*-acylglyceramides **5**

By suitable manipulation of the glyceramide framework in **5**, the method can be used to create new families of synthetic amphiphilic compounds having potential applications as surfactantactive compounds and as carriers for drug encapsulation and delivery.

Simple α-diazoketones proved refractory to the standard conditions of the Passerini or Ugi condensations, even when heated to 60–70 °C. However, α-diazoketones and sulfonic acids spontaneously formed β-ketosulfonates, a family of reactive carbonyls that were recently utilized in a new Ugi-based approach to substituted 2-oxazolines.[5]

3.2 Results and Discussion

We therefore investigated two-stage, one-pot MCRs of the representative diazoketone **1a** (Scheme 3.2) triggered by an initial metal-catalyzed insertion into a typical carboxylic acid (e.g., HOAc),[6,7] followed by an *in situ* Passerini condensation as shown. With $Rh_2(OAc)_4$ as catalyst, complex product mixtures were formed from which only minor quantities of the initial insertion product 1-acetoxy-4-phenyl-2-butanone **6a** could be isolated. However, using $Cu(acac)_2$ (10 mol %),[7] the desired di-*O*-acylglyceramide **5a** was obtained in 68% yield, along with **6a** (26%).



Scheme 3.2 Synthesis of Substituted Di-*O*-acylglyceramides **5a**

Optimization of this 4-component reaction led to several interesting findings. To begin with, Shinada et al. used relatively large quantities of $Cu(acac)_2$ (10 mol %) for the initial diazoketone insertion reaction, raising the concern that copper complexation of the isonitrile component might cause a sequestering effect that would interfere with the subsequent Passerini condensation leading to **5**. To investigate this question, a pure sample of 1-acetoxy-4-phenyl- 2-butanone **6a** was subjected to the Passerini reaction leading to **5a** with and without $Cu(acac)_2$ (5 mol %), and the progress of the condensation was monitored by following disappearance of the ketoacetate, as shown in Figure 3.1.

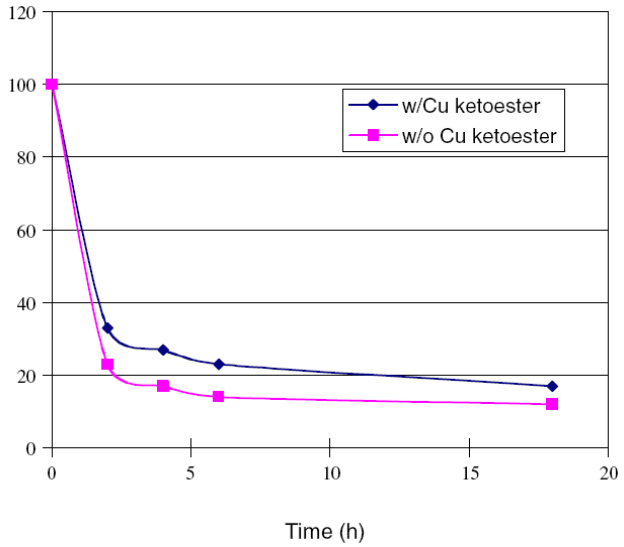


Figure 3.1 Effects of $Cu(acac)_2$ on the Formation of **5a**

As the data in Figure 3.1 illustrate, $Cu(acac)_2$ exerted a mild rate retarding effect on the formation of **5a**. A similar effect was also noted in Passerini reactions of the parent ketone, 4-phenyl-2-butanone, which suggested that complexation by $Cu(acac)_2$ depleted the reaction medium of the key of the isonitrile reactant. Besides explaining the modest yield of **5a**, isonitrile sequestration by copper also accounted for the recovery of significant quantities of unreacted ketoacetate **6a**.

One successful solution to the problem involved using excess isonitrile. However, to optimize the synthetic efficiency of the process we investigated whether lower catalyst loads might also improve the yields of **5**. Dropwise addition of diazoketone **1a** (1.3 equiv) into a toluene solution (60 °C, 30 min) of acetic acid and 1.0 mol % of $Cu(acac)_2$ followed by in situ Passerini condensation afforded **5a** in 94% yield. Upon further experimentation, we observed that the diazoketone insertion reaction could be achieved equally well in most cases without any metal catalyst, although the somewhat higher temperatures required (100–110 °C) led us to favor the use of 1 mol % $Cu(acac)_2$ in most circumstances.

Table 3.1 summarizes the scope and versatility of the new four component synthesis of di-*O*-acylglyceric acid diamides depicted in Scheme 3.1, which has been successfully implemented as a one-pot process.

Table 3.1 $Cu(acac)_2$-Catalyzed 4-Component Condensations of R_1COCHN_2, R_2CO_2H, R_3NC, and R_4CO_2H Leading to **5**

1 R_1=	**2** R_2=	**3** R_3=	**4** R_4=	Product Yield (%)
$Ph(CH_2)_2$ **1a**	CH_3	*t*-Bu	CH_3	**5a** (94)
1a	CH_3	*t*-Bu	$(CH_3)_2CH$	**5b** (90)
1a	Ph	EtO_2CCH_2	C_7H_{15}	**5c** (72)
C_7H_{15} **1b**	$(CH_3)_2CH$	*t*-Bu	$CbzNHCH_2$	**5d** (70)
1b	Ph	*cyclo*-C_6H_{11}	CH_3	**5e** (80)
cyclo-C_6H_{11} **1c**	C_7H_{15}	*n*-Bu	CH_3	**5f** (70)
1c	$NCCH_2$	EtO_2CCH_2	Ph	**5g** (76)
CH_3 **1d**	$(CH_3)_2CH$	*n*-Bu	$CbzNHCH_2$	**5h** (71)
1d	$H(CH_2OCH_2)_3$	*t*-Bu	C_7H_{15}	**5i** (58)

The initial insertion reactions were monitored by N_2 evolution and usually required heating for 30–60 min at 60–90 °C. In reactions using diazoketones **1a–c**, 1.3 equiv of diazoketone was used, whereas insertions using diazoacetone **1d** were optimally achieved using 1.8 equiv of diazoketone. The scope of the new four-component condensation appears to be limited to aliphatic diazoketones. In the case of benzoyldiazomethane, the initial insertion was successful, but the α-acyloxyketone failed to undergo the subsequent Passerini reaction.

The product glyceramides **5** were formed as racemic mixtures. With respect to controlling the new stereogenic center formed in the second step of the MCR, we were intrigued by a recent paper by Andreana et al., reporting that certain a-substituted aldehydes capable of bidentate binding underwent enantioselective Passerini reactions using an indan (pybox) Cu(II) Lewis acid complex.[8] Using the synthesis of **5 h** as a test case, diazoketone **1d** was reacted with isobutyric acid in the absence of $Cu(acac)_2$ to form the corresponding acyloxypropanone. The subsequent Passerini reaction was conducted in the presence of indan (pybox) Cu(II) catalyst (20 mol %) following the protocol of Andreana et al. and produced **5 h** with no measurable enantiomeric excess.

3.3 Conclusion

The new MCR represents a more selective and efficient alternative to the stepwise introduction of carboxylic ester groups into the *vic*-diol backbone of glyceramides, since it avoids the potential for ester interchange by competing *O*,*O*-acyl transfer side reactions. As one illustration of its utility, we describe the synthesis of a 'facially amphiphilic'[9] diester **5i** containing one lipophilic and one hydrophilic side chain, each derived from a carboxylic acid.

3.4 Experimental Procedures

^{1}H NMR and ^{13}C NMR were taken on a Varian Mercury-300,Varian Inova-400 or Varian Inova-500 spectrometer as indicated using $CDCl_3$ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and were referenced to residual TMS (0.00 ppm for ^{1}H NMR) and $CDCl_3$ (77.23 ppm for ^{13}C NMR). IR spectra were obtained on a Thermo Nicolet Avatar 370 DTGS spectrometer and were recorded in wavenumbers (cm^{-1}). Chemicals were obtained from Aldrich, Fluka, Fisher, Mallinckrodt and used as received unless specified. In reactions leading to diastereomers, spectroscopic data were reported for mixtures, unless specified otherwise.

Representative experimental procedure for diester **5b**: A mixture of acetic acid (57 μL, 1.0 mmol) and $Cu(acac)_2$ (2.6 mg, 0.01 mmol, 1 mol %) in toluene (2 mL) in a 10 mL round bottomed flask was heated to 60 °C for 10 min under nitrogen. To it was added dropwise a solution of diazoketone **1a** (226 mg, 1.3 mmol, 1.3 equiv) in toluene (2 mL). Once gas evolution was judged complete, the reaction mixture was stirred for an additional 5 min, then cooled and concentrated in vacuo. The oily residue was blanketed in nitrogen, then treated with *iso*-butyric acid (140 μL, 1.5 mmol, 1.5 equiv) and *t*-BuNC (170 μL, 1.5 mmol, 1.5 equiv). The resulting reaction mixture was stirred at rt under N_2 for 20 h. The product was purified by flash column chromatography (1:1 EtOAc/hexanes, Rf = 0.3) to afford **5b** (338 mg, 90%) as a pale yellow oil.

*Compound **5b***: The crude product obtained was purified by silica gel flash column chromatography (1:1 hexanes: ethyl acetate, Rf= 0.4) to afford **5b** as a yellow oil (279 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.28 (m, 5 H), 6.39 (s, 1 H), 4.90 (d, 1 H, J= 11.5 Hz), 4.42 (d, 1 H, J= 11.5 Hz), 2.46-2.61 (m, 4 H), 2.28 (m, 1 H), 2.02 (s, 3 H), 1.41 (s, 9 H), 1.20 (dd, 6 H, J= 7.0, 2.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.53, 170.15, 168.63, 140.86, 128.71, 128.67, 126.40, 85.74, 64.98, 51.64, 35.05, 33.35, 29.72, 28.93, 20.86, 19.35, 19.21; IR (neat) 3438(s), 2970(s), 1745(s), 1691(s); CIMS (methane) m/z: 378.3 (M+H), 308.2, 209.2.

*Compound **5c***: The crude product obtained was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, Rf= 0.3) to afford **5c** as a pale yellow oil (347 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 2 H), 7.12-7.58 (m, 8 H), 5.24 (d, 1 H, J= 11.7 Hz), 4.64 (d, 1 H, J= 11.7 Hz), 4.24 (q, 2 H, J= 7.2 Hz), 4.10 (t, 2 H, J= 6.3 Hz), 2.61 (m, 2 H), 2.22-2.46 (m, 4 H), 1.61 (m, 2 H), 1.10-1.40 (m, 13 H), 0.88 (t, 3 H, J= 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.62, 170.22, 169.72, 165.72, 140.65, 133.36, 129.89, 129.81, 128.72, 128.62, 128.58, 126.33, 85.96, 65.27, 61.92, 41.62, 35.14, 34.09, 33.49, 31.83, 31.76, 29.72, 29.22, 29.11, 25.13, 24.90, 22.79,

22.78, 14.35, 14.27, 14.24; IR (neat) 3389(b), 2935(s), 2852(s), 1745(s), 1727(s), 1684(s); CIMS (methane) m/z: 526.3 (M+H), 400.2, 382.2.

*Compound **5d***: The crude product obtained was purified by silica gel flash column chromatography (3:7 hexanes: ethyl acetate, Rf= 0.3) to afford **5d** as a pale yellow oil (365 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 6.31 (s, 1 H), 5.26 (t, 1 H, J= 5.0 Hz), 5.13 (s, 1 H), 4.90 (d, 1 H, J= 11.8 Hz), 4.37 (d, 1 H, J= 11.8 Hz), 3.96 (t, 2 H, J= 6.6 Hz), 2.52 (m, 1 H), 2.19 (m, 1 H), 1.95 (m, 1 H), 1.58 (s, 2 H), 1.37 (s, 9 H), 1.24 (b, 10 H), 1.13 (dd, 6 H J= 7.0, 2.3 Hz), 0.86 (t, 3 H, 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.60, 168.22, 167.72, 156.54, 136.17, 128.80, 128.55, 128.31, 87.53, 67.48, 64.48, 51.73, 43.70, 34.11, 32.11, 31.87, 29.44, 29.19, 28.82, 22.99, 22.78, 19.20, 19.11, 14.29; IR (neat) 3422(m), 3339(b). 2961(s), 2927(s), 2857(s), 1735(s), 1672(s); CIMS (methane) m/z: 521 (M+H), 413, 312.

*Compound **5f***: The crude product obtained was purified by silica gel flash column chromatography (1:1 hexanes: ethyl acetate, Rf= 0.3) to afford **5f** as a clear oil (70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (t, 1 H, J= 5.0 Hz), 4.96 (d, 1 H, J= 11.5 Hz), 4.69 (d, 1 H, J= 11.5 Hz), 3.29 (q, 2H, J= 7.2 Hz), 2.26 (t, 3 H), 2.12 (s, 3 H), 1.0-1.80 (m, 30 H), 0.80-1.00 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.96, 168.85, 87.52, 63.38, 41.90, 39.24, 34.32, 31.78, 29.15, 29.08, 27.55, 27.32, 26.54, 26.41, 26.18, 25.09, 22.73, 22.06, 20.21, 14.18, 13.86; CIMS (methane) m/z: 412 (M+H), 370, 352, 268.

*Compound **5g***: The crude product obtained was purified by silica gel flash column chromatography (1:1 hexanes: ethyl acetate, Rf= 0.4) to afford **5g** as a clear oil (337 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2 H, J= 5.0 Hz), 7.44-7.66 (m, 3 H), 6.99 (t, 1 H, J= 5.0 Hz), 5.26 (d, 1 H, J= 11.5 Hz), 5.00 (d, 1 H, J= 11.5 Hz), 4.24 (q, 2H, J= 7.2 Hz), 4.12 (dd, 2H, J= 3.5, 1.5 Hz), 3.40 (s, 2 H), 2.46 (m, 1 H), 1.75-1.88 (m, 4 H), 1.10-1.40 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.97, 169.34, 165.11, 162.50, 134.18, 130.25, 130.09, 129.27, 113.12, 88.23, 66.17, 62.20, 42.39, 41.82,

27.95, 27.59, 26.74, 26.61, 26.37, 25.02, 14.59; IR (neat) 3426(s), 2930(s), 2854(s), 1757(s), 1726(s), 1683(s); CIMS (methane) m/z: 445 (M+H), 360, 323.

*Compound **5h***: The crude product obtained was purified by silica gel flash column chromatography (1:1 hexanes: ethyl acetate, Rf= 0.3) to afford **5h** as a pale yellow oil (71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.40 (m, 5 H), 6.54 (s, 1 H), 5.30 (s, 1 H), 5.13 (q, 2 H), 4.71 (dd, 1H), 4.43 (dd, 1H), 3.93 (m, 2 H), 3.26 (m, 2 H), 2.53 (m, 1 H), 1.68 (s, 3 H), 1.51 (m, 2 H), 1.35 (m, 2 H), 1.14 (d, 6 H), 0.93 (t, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.55, 169.75, 168.10, 156.91, 136.11, 128.81, 128.58, 128.25, 83.85, 67.52, 65.48, 43.83, 39.60, 34.06, 31.67, 20.32, 20.23, 19.13, 19.06, 13.96; IR (neat) 3336(s), 2953(s), 2927(s), 1738(s), 1659(s), 1536(s); CIMS (methane) m/z: 437 (M+H), 393, 349.

*Compound **5i***: The crude product obtained was purified by silica gel flash column chromatography (1:1 hexanes: ethyl acetate, Rf= 0.2) to afford **5i** as a pale yellow oil (58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1 H), 4.80 (dd, 1H), 4.48 (dd, 1H), 4.13 (d, 2 H), 3.55-3.75 (m, 8 H), 3.38 (s, 3 H), 2.34 (t, 2 H), 1.64 (s, 3 H), 1.5-1.7 (s, 4 H), 1.36 (s, 9 H), 1.20-1.40 (s, 8 H), 0.89 (t, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.72, 169.82, 169.32, 82.27, 72.05, 71.12, 70.81, 70.72, 68.48, 65.92, 59.23, 51.46, 35.18, 31.82, 29.17, 29.13, 28.75, 25.09, 22.78, 20.00, 14.26; IR (neat) 3512(s), 3445(s), 2957(s), 2927(s), 2867(s), 1745(s), 1678(s); CIMS (methane) m/z: 462 (M+H), 336, 318, 284.

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CHAPTER FOUR

Studies on the Chemistry and Reactivity of α-Substituted Ketones in Isonitrile-Based Multicomponent Reactions

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Journal of Organic Chemistry **2008**, *73*, 9720–9726

4.1 Introduction

The discovery in 1850 that α-amino acids could be prepared in one step from simple reactants using the Strecker reaction, the first reported example of a multicomponent reaction, launched a period of intensive synthetic chemical development that remains active today. Generally defined as one-pot processes that produce a desired target from the combination of three or more reactants,[1] MCRs can create simple and convergent paths to structurally complex products in atom-economical[2] fashion. With the advent of combinatorial chemistry and its widespread adoption by the pharmaceutical industry, MCR chemistry experienced a renaissance of interest in the past two decades, triggered initially by the demand for screening libraries in drug discovery programs, and stimulated more recently by efforts to assemble natural product-like scaffolds exhibiting specific pharmacological profiles.

To date, MCR reactions based on the chemistry of isonitriles have been particularly widely used in these endeavors, despite the well-known drawbacks to using this family of compounds. Besides their unpleasant olefactory properties, isonitriles have generally been limited in their commercial availability and have limited shelf stability. In recent years, however, versatile new syntheses of isonitriles have been developed,[3] including routes to convertible isonitriles possessing pleasant aromas,[4] that promise to expand the repertoire of known MCRs.

The Passerini and Ugi reactions, which represent the two most widely employed isonitrile-based MCRs, also need simple carbonyl compounds as integral reactants. As part of our efforts to synthesize new molecular frameworks by using the "single reactant replacement" (SRR) strategy to evolve existing MCRs, we have investigated aldehydes and ketone surrogates that combine carbonyl electrophilic properties with additional embedded reactivity elements. For example, we recently discovered that replacing simple carbonyl compounds in the Passerini reaction with

acyl cyanides made it possible to redirect the outcome to afford β-aminoacid diamides instead of the conventional α-acyloxyamides,[5] and further empowered the assembly of densely functionalized oxazoles and tetrazoles.[6]

We also investigated the use of α-diazoketones in isonitrile based MCRs, finding them resistant to Passerini and Ugi reactions. However, by exploiting the reactivity of diazocarbonyls to Bronsted acids or transition metal catalysis, we recently achieved successful one-pot, four-component condensations that furnished substituted oxazolines via α-sulfonyloxyketones[7] as well as substituted di-*O*-acylglyceramides from α-acyloxyketones.[8] Following those communications, we now report a full account of our studies using α-substituted ketones as surrogates for simple carbonyl compounds in the Ugi and Passerini reactions.

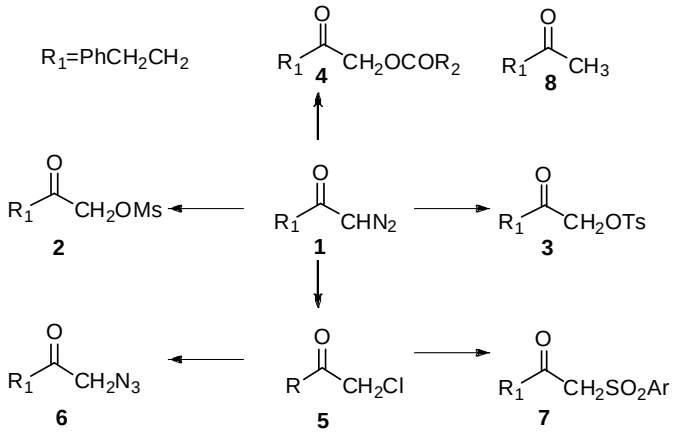
The rationale for this study was to investigate SRR outcomes when reactive functionality was embedded at the α-position of the ketone. While several reactive α-substituents were of potential interest (sulfonyloxy, acyloxy, azido, halo, hydroxyl and sulfonyl), almost nothing was known about their MCR chemistry, let alone relative reactivities. Prior to our own oxazoline-forming synthesis, there were no reports of Passerini or Ugi condensations on α-mesyloxy- or tosyloxyketones. Likewise, no examples of MCRs of α-azido-, α-hydroxy-, or α-sulfonylketones have been described in the literature. Enantioselective, copper-catalyzed Passerini reactions of alkoxysubstituted aldehydes have recently been described,[9] but no examples of the corresponding alkoxyketones were included. α-chloroketones have been reported to undergo the Passerini condensation, forming chloro-substituted acyloxyamides, which after subsequent base treatment were transformed into the corresponding acyloxy-*β*-lactams.[10]

It occurred to us that any pronounced rate differences between these various substituted ketones might make it possible to achieve selectivity when using mixtures

of two or more carbonyl compounds, thus broadening the opportunities for incorporating novel functionality in MCRs. Anchimeric effects involving the neighboring α- substituent might also be exploited to produce new molecular frameworks. Here we report the relative rates of condensation of a representative series of α-substituted ketones in the Passerini condensation. That kinetic study provides useful new insights into the relative reactivity of each family and suggests additional directions for new work.

4.2 Results and Discussion

Preparation of Substrates. The starting material for all α-substituted ketones was the corresponding α-diazoketone **1** (Scheme 4.1), which could be conveniently prepared by reaction of the cognate acid chloride with diazomethane. Initially, the readily available 1-diazo-4-phenyl-2-butanone **1a** (prepared from hydrocinnamoyl chloride) was used to synthesize a representative example of each family of substituted ketones. Reaction of **1a** with methanesulfonic acid or toluenesulfonic acid furnished the mesyloxy and tosyloxyketones **2a** and **3a**, respectively.[11] The corresponding acyloxyketone **4a** ($R_2 = CH_3$) was prepared from **1a** by $Cu(acac)_2$-catalyzed reaction with acetic acid.[12] Chloroketone **5a** was obtained from **1a** by reaction with HCl in ether.[13]



Scheme 4.1 Preparation of Substrates

Azidoketones **6** and arylsulfonylketones **7** were both prepared according to literature methods from the corresponding chloroketones **5**. Thus, azidoketone **6a** arose from the reaction of **5a** with NaN_3 in DMF.[14] The synthesis of α-sulfonylketone **7a** (Ar = Ph) was achieved by reaction of **5a** with thiophenol and NaOH in the presence of oxone.[15] A sample of the parent unsubstituted ketone, benzylacetone **8a**, was obtained commercially and used as a control compound for the kinetic study.

Relative Rate Study of α-Substituted Ketones in the Passerini Reaction. Compounds **2a** and **4a**-**8a** were subjected to a representative Passerini condensation with acetic acid and *t*-butyl isonitrile (1.0 equiv each) under neat conditions at rt. Aliquots of each reaction mixture were removed for NMR analysis, and the progress of the reaction was monitored by the relative amounts of starting ketone (as judged by integration of the singlet resonance for the α-methylene carbon) and the Passerini product (as measured by the AB-quartet for the same methylene group). The results are tabulated in Figure 4.1.

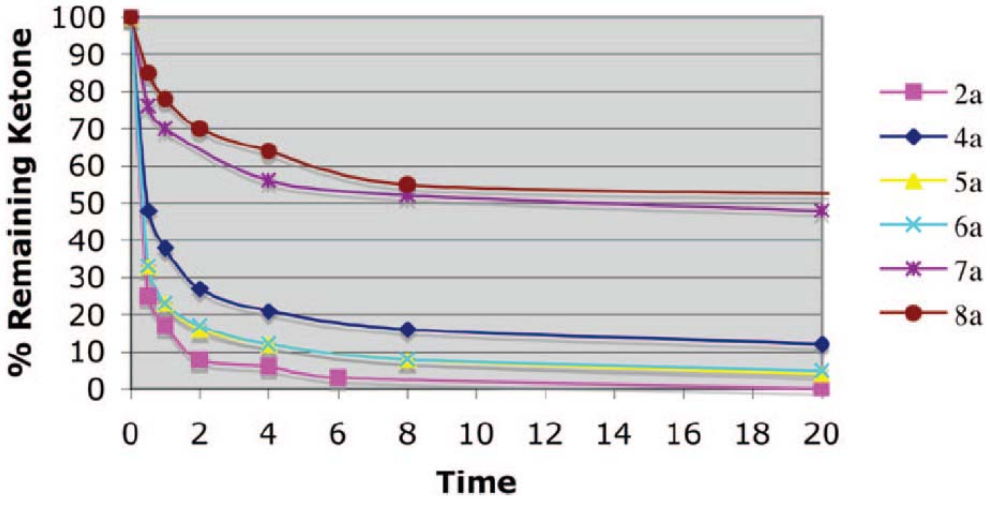
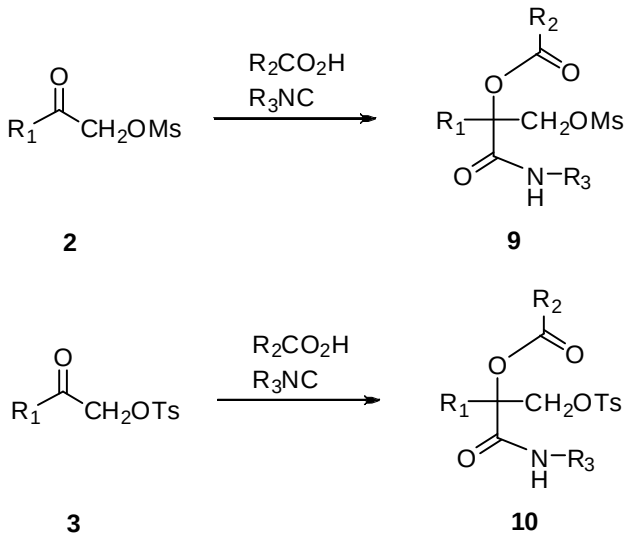


Figure 4.1 Relative Rates of a Representative Passerini Condensation of α-Substituted Ketones.

As the data indicate, each of the α-substituted ketones underwent Passerini condensation more rapidly than the parent carbonyl compound **8a**. Mesyloxyketone **2a** was the most reactive carbonyl compound tested. Although tosylate **3a** was not included in the rate study, independent side-by-side comparisons of **2a** and **3a** in other Passerini and Ugi condensations (*vide infra*) established that **3a** displayed comparable reactivity in isonitrile-based MCRs. Chloroketone **5a** and azidoketone **6a** showed similar rate profiles, and were somewhat more reactive than acyloxyketone **4a**. Sulfonylketone **7a** was the least reactive of the substituted ketones tested, undergoing Passerini condensation only slightly faster than **8a**. The kinetic data in Figure 4.1 were consistent with the expected enhancement of carbonyl electrophilicity caused by electronegative substituents, as judged by known Pauling atom or group electronegativity values for each of the substituents tested.[16] Results with compounds **2a**, **5a**, and **6a** suggested that selective Passerini condensations on these substances might be possible in the presence of a sulfonyl-substituted or unsubstituted ketone. As a preliminary test of this hypothesis, a 1:1 mixture of chloroacetone **5b** ($R_1 = CH_3$) and phenylsulfonylacetone **7b** ($R_1 = CH_3$) were reacted with 1 equiv each of acetic acid and *t*-butyl isonitrile (24 h, rt) to afford an 8:1 ratio of products from **5b** and **7b**, respectively.

Isonitrile-Based MCRs of Substituted Ketones. Mesyloxy and tosyloxyketones **2** and **3** proved to be very good carbonyl components in the Passerini reaction, typically forming the expected products **9** and **10**, respectively, in high yields (Scheme 4.2).



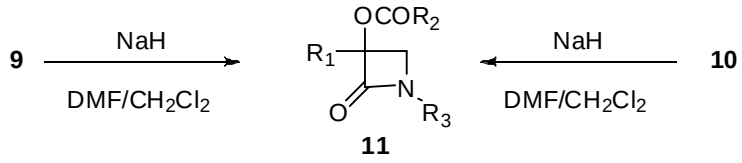
Scheme 4.2 Passerini Reaction of Mesyloxy- and Tosyloxyketones

The results of a representative sampling of condensations using various carboxylic acids and isonitriles (1.1 equiv each) are summarized in Table 4.1. Condensations of **2** and **3** were generally completed in 12-18 h and successfully furnished the expected products in very good to excellent yields. Products **9** and **10** were readily purified by flash column chromatography. Furthermore, the possibility of directly converting the parent α-diazoketone to mesylate **9a** was realized in a simple one-pot process by reacting a CH_2Cl_2 solution of diazoketone **1a** with methanesulfonic acid (1.1 equiv, 10 min, 0 °C). After addition of NaOAc (0.5 equiv) to neutralize residual acid, the solution was treated with acetic acid and cyclohexyl isonitrile (rt 24 h) to afford **9a** in 86% yield.

Table 4.1 Passerini Reactions of Mesyloxy- and Tosyloxyketones

mesylate/tosylate R_1=	R_2CO_2H R_2=	R_3NC R_3=	Product (Yield)
2a $Ph(CH_2)_2$	CH_3	*t*-Bu	**9a** (88%)
2a	Ph	*cycle*-C_6H_{11}	**9b** (82%)
2a	CH_3	*cycle*-C_6H_{11}	**9c** (80%)
2b *n*-C_7H_{15}	CH_3	*cycle*-C_6H_{11}	**9d** (91%)
2c *cycle*-C_6H_{11}	Ph	*n*-Bu	**9e** (80%)
2d Ph	CH_3	*cycle*-C_6H_{11}	**9f** (18%)
3a $Ph(CH_2)_2$	Ph	*t*-Bu	**10a** (99%)
3a	Ph	*cycle*-C_6H_{11}	**10b** (97%)
3b *n*-C_5H_{11}	CH_3	*cycle*-C_6H_{11}	**10c** (97%)
3b	Ph	*cycle*-C_6H_{11}	**10d** (99%)
3c *cycle*-C_6H_{11}	CH_3	*t*-Bu	**10e** (80%)
3d Ph	Ph	*cycle*-C_6H_{11}	**10f** (28%)

With their reactive sulfonate leaving groups, sulfonates **9** and **10** were also well-suited precursors for the synthesis of substituted β-lactams **11** (Scheme 4.3) following a procedure developed for cyclizations of the corresponding chloro compounds.[10]



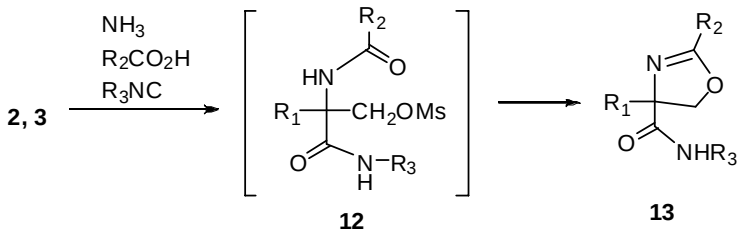
Scheme 4.3 Synthesis of Acyloxy-β-lactams **11** from Mesyloxy- and Tosyloxyketones

Table 4.2 summarizes results obtained in our laboratory using this approach to substituted β-lactams from representative sulfonates **9** and **10**. While the yields of **11a-e** were generally comparable whether from the mesylate or tosylate precursor, the cyclization was noticeably more rapid in the case of mesylate **9c**.

Table 4.2 Synthesis of Acyloxy-β-lactams **11** from Sulfonates **9** and **10**

sulfonate	product (yield)
9c	**11a** (62%)
10a	**11b** (46%)
10b	**11c** (59%)
10c	**11d** (64%)
10d	**11e** (56%)

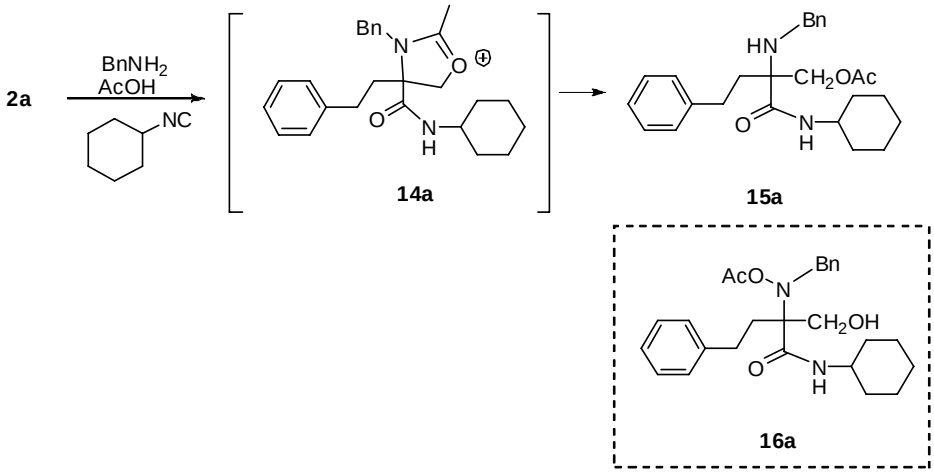
We also investigated Ugi reactions of sulfonyloxyketones **2** and **3**. When using ammonia as the amine, the MCR led to a novel 4-component synthesis of substituted 2-oxazolines **13** (Scheme 4.4) by way of the intermediate diamides **12**.[7] Apparently the formation of imines derived from **2** or **3** was faster than ammonolysis of the mesylate or tosylate group, thus triggering the desired Ugi reaction to form **12**. The fact that **12** cyclized spontaneously to **13** during the reaction finds precedent in the known biosynthesis of peptide-based oxazolines[17] by cyclization of activated N-acylserine derivatives.[18]



Scheme 4.4 Synthesis of Oxazoline **13** from Sulfonates **9** and **10**

Initial studies of this interesting transformation with **2a** as a representative mesyloxyketone utilized methanol as solvent, a common medium for Ugi condensations, and also afforded significant quantities of the corresponding Passerini product **9**. This byproduct could be effectively suppressed by replacing methanol with 2,2,2-trifluoroethanol, a solvent that was recently reported to improve Ugi reactions involving ammonia as the amine component.[19] Overall, the new oxazoline synthesis, for which full experimental details on 14 examples have been reported,[7] accommodated a broad range of sulfonyloxyketones, isonitriles and carboxylic acids.

Our initial communication noted that when NH_3 was replaced with benzylamine, the MCR of **2a** with acetic acid and cyclohexyl isonitrile afforded aminoester **15a** (Scheme 4.5) as the exclusive product. Particularly characteristic was the strong ester carbonyl band (1740 cm^{-1}) in the IR spectrum of **15a**.



Scheme 4.5 Ugi Reactions of Mesyloxyketones **2** with Primary Amines

A mechanism of formation of **15a** paralleling that of **13** could be envisioned in which hydrolysis of the oxazolinium intermediate **14a** led to the observed product. Interestingly, **15a** did not undergo 1,2-acyl shift, leading to the corresponding

amidoalcohol **16a**. Further confirmation of the structure of **15a** was obtained by single crystal X-ray diffraction analysis.

Structures such as **16a** embody the hydroxyethylene or hydroxyethyl structural unit found in transition state isosteres such as statine or norstatine, which have been developed as inhibitors of retroviral proteases.[20] Given their potential biomedical significance, we have investigated this MCR further. As indicated in Table 4.3, several other primary amines and mesyloxyketones formed the corresponding amidoesters **15**. In each case, only the amidoester isomer **15** (and none of the diamide **16**) was detected.

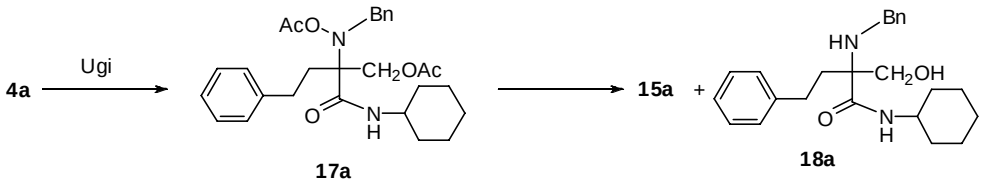
Table 4.3 Ugi Reactions of Mesyloxyketones **2** with Primary Amines

mesylate **2**	R_2CO_2H	R_3NH_2	R_4NC	Product
R_1=	R_2=	R_3=	R_4=	(Yield)
2a $Ph(CH_2)_2$	CH_3	Bn	*cycle*-C_6H_{11}	**15a** (71%)
2a	*i*-Pr	allyl	*cycle*-C_6H_{11}	**15b** (66%)
2b *n*-C_7H_{15}	Ph	Bn	*t*-Bu	**15c** (67%)
2b	*i*-Pr	allyl	*cycle*-C_6H_{11}	**15d** (61%)
2b	CH_3	*i*-Pr	*cycle*-C_6H_{11}	**9e** (70%)
2c *cycle*-C_6H_{11}	*i*-Pr	*n*-Bu	*t*-Bu	**15e** (39%)
2d CH_3	CH_3	Bn	*t*-Bu	**15f** (74%)

To determine whether the products observed in each case were formed under kinetic control, aminoester **15a** was subjected to basic (DBU-CH_3CN, Et_3N, NaH-DMF) equilibration conditions. However, no evidence for the formation of diamide **16a** was obtained from these experiments.

The complementary equilibration experiment required an authentic sample of **16a**, which we attempted to synthesize from acetoxyketone **4a** in two steps using the

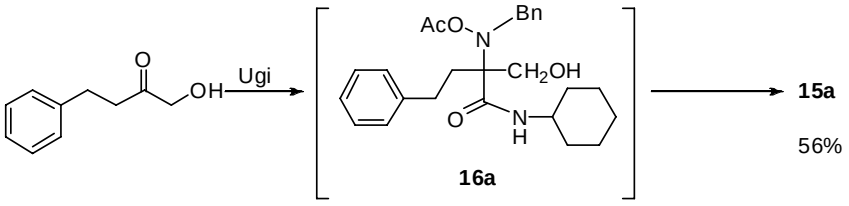
Ugi reaction as shown below (Scheme 4.6). Little is known about Ugi condensations of such acyloxyketones. In fact, reaction of **4a** with ammonia, acetic acid, and cyclohexyl isonitrile returned mostly starting ketoacetate **4a**, along with the corresponding Passerini product **(**not shown) in 14% yield. However, replacing ammonia with benzylamine did afford the desired MCR product **17a** in 67% yield.



Scheme 4.6 Hydrolysis of the Ugi Product **17a**

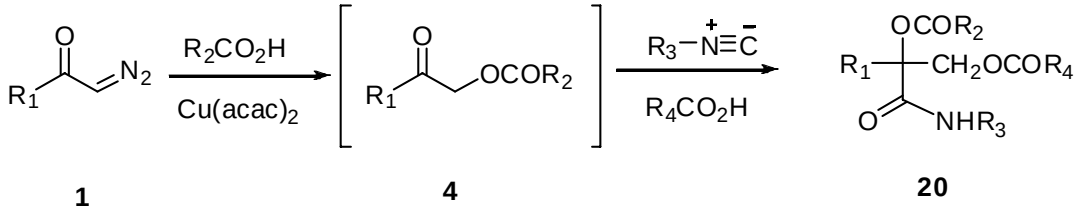
Treatment of **17a** with NH_3-CH_3OH was expected to furnish **16a** by methanolysis of the more reactive acetate ester. Instead, two products were formed: aminoester **15a** (20%) and aminoalcohol **18a** (60% yield). Unfortunately, none of the hoped for amidoalcohol **16a** could be detected by IR.

In an alternative approach (Scheme 4.7), the known[21] hydroxyketone **19** was subjected to the Ugi reaction with benzylamine, acetic acid and cyclohexyl isonitrile. Instead of the expected amidoalcohol **16a**, the sole product of that reaction (56%) was aminoester **15a**. Taken together, the results depicted in Schemes 6 and 7, while not conclusive, were consistent with the rapid conversion of **16a** to **15a** and its hydrolysis product **18a**.



Scheme 4.7 Ugi Reaction of β-Hydroxy Ketone **19**

It became apparent from efforts to prepare **16a** that Ugi condensations of acyloxyketones **4**, while feasible, suffered certain limitations. Therefore, we decided to study the reactivity of acyloxyketones in the corresponding Passerini reactions. A recently published preliminary report summarized our findings in this area.[8] Since acyloxyketones of general structure **4** were easily prepared by copper-catalyzed insertion of diazoketone **1** into a carboxylic acid,[22] we were able to develop a versatile one-pot 4-component condensation in two stages leading to a new family of structurally diverse di-O-acylglyceric acid amides **20** (Scheme 4.8).



1 **4** **20**

Scheme 4.8 Four-Component Condensations of Diazoketone **1** Leading to Di-*O*-acylglyceric Acid Amides **20**

The initial insertion stage required heating of **1** with R_2CO_2H (30-60 min, toluene, 60-90 °C), usually in the presence of 1.0 mol % $Cu(acac)_2$. Once gas evolution ceased, the toluene was removed in vacuo and the crude acyloxyketone **4** was subjected to a Passerini condensation with R_3NC and R_4CO_2H. Table **4.4** summarizes the range of new glyceramide diesters thatcould be synthesized using this method.

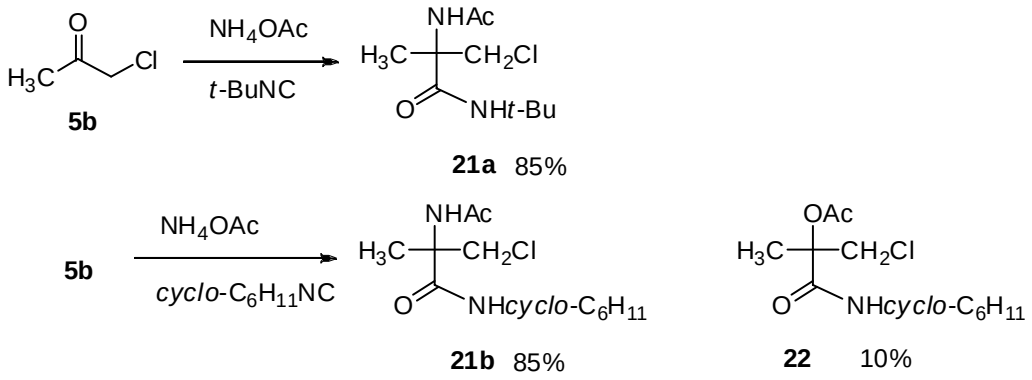
Table 4.4 Four-Component Condensations of Diazoketone **1** Leading to Di-*O*-acylglyceric Acid Amides **20**

	R_2CO_2H	R_3NC	R_4CO_2H	Product
1 R_1=	**2** R_2=	**3** R_3=	**4** R_4=	(Yield)
$Ph(CH_2)_2$ **1a**	CH_3	*t*-Bu	CH_3	**20a** (94%)
1a	CH_3	*t*-Bu	$(CH_3)_2CH$	**20b** (90%)
1a	Ph	EtO_2CCH_2	C_7H_{15}	**20c** (72%)
C_7H_{15} **1b**	$(CH_3)_2CH$	*t*-Bu	$CbzNHCH_2$	**20d** (70%)
1b	Ph	*cyclo*-C_6H_{11}	CH_3	**20e** (80%)
cyclo-C_6H_{11} **1c**	C_7H_{15}	*n*-Bu	CH_3	**20f** (70%)
1c	$NCCH_2$	EtO_2CCH_2	Ph	**20g** (76%)
CH_3 **1d**	$(CH_3)_2CH$	*n*-Bu	$CbzNHCH_2$	**20h** (71%)
1d	$H(CH_2OCH_2)_3$	*t*-Bu	C_7H_{15}	**20i** (58%)

One advantage of the method over stepwise acylation of the *vic*-diol moiety in glyceramides is that it avoids the potential for ester interchange by competing *O,O*-acyl transfer side reactions. Moreover, by using one hydrophobic and one hydrophilic carboxylic acid (e.g., **20i**), the approach depicted in Scheme 8 can be used to synthesize facially amphiphilic glyceramides for potential biomedical use, whether as cell wall disrupting agents displaying antifungal activity or as encapsulating agents in micellar drug delivery. The method can be adapted to introduce different chain lengths in each ester group to fine tune desired hydrophobic/hydrophilic properties.

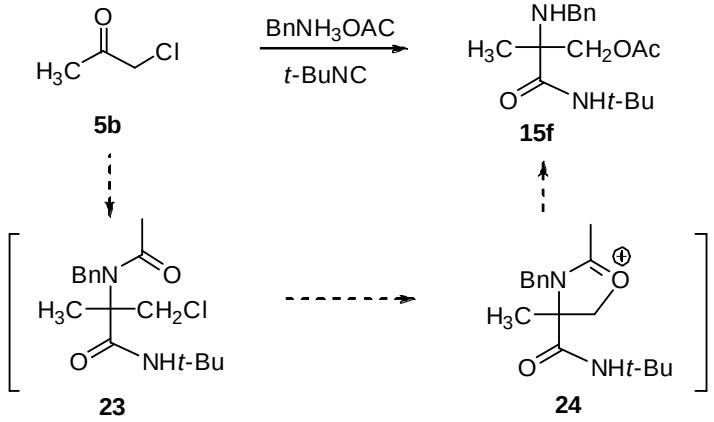
The use of α-chloroketones **5** in isonitrile-based multicomponent reactions were also of interest in this investigation. Since Passerini reactions of **5** have already been described,[10] we turned our attention to Ugi 4-component condensations of

chloroacetone **5b** (R = CH_3) as a representative chloroketone using conditions optimized for the corresponding mesyloxyketones **2**. Thus, reaction of **5b** with ammonium acetate (4 equiv) and *t*-butyl isonitrile (1.1 equiv, rt, 24 h) in trifluoroethanol solvent afforded the normal Ugi product **21a** in very good yield. Likewise, condensation of **2b** with NH_4OAc and cyclohexyl isonitrile also afforded the expected Ugi product **21b**, along with small quantities of the corresponding Passerini product **22**, Scheme 4.9.



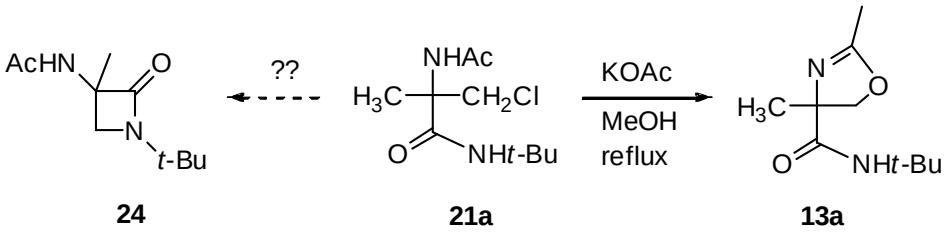
Scheme 4.9 Ugi Reaction of Chloroketone **5b**

Using benzylamine instead of ammonia, the Ugi condensation of **5b** took a different path, forming aminoester **15f** (Scheme 4.10) in 74% yield, along with a small amount of the corresponding Passerini product (14%, structure not shown). As depicted in Scheme 4.10, the formation of aminoester **15f** likely proceeded by an initial Ugi reaction leading to **23**, followed by a rearrangement via **14f** similar to that invoked for related structures **15a-e** (Scheme 4.5).



Scheme 4.10 Ugi Reaction of Chloroketone **5b** with Benzylamine

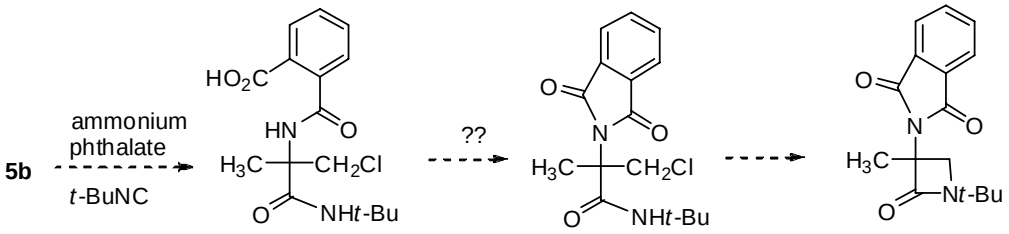
Chloroketone-derived Ugi products like **21a** and **21b** would be particularly useful if they underwent cyclization to the corresponding acylamino-β-lactams **24** (Scheme 4.9, 4.11), which embody the key structural element of penicillins, cephalosporins, and other β-lactam antibiotics at the forefront of modern antimicrobial chemotherapy.[23] Not surprisingly, however, exposure of **21a** to mild base instead formed the known[17] oxazoline **13a**.



Scheme 4.11 Cyclization of Ugi Product **21a**

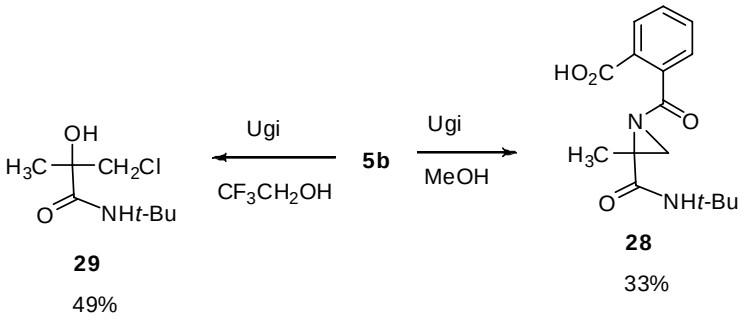
We reasoned that replacing the acetamide group in **21a** with a phthalimide would block the undesired formation of an oxazoline. Moreover, if the Ugi condensation of **5b** using phthalic acid in combination with ammonia and *t*-

butylisonitrile were successful, the initally formed phthalimidic acid **25** (Scheme 4.12) might spontaneously dehydrate to the phthalimide **26** either during workup or upon standing, thus paving an approach to the desired β-lactam **27**.



Scheme 4.12 Ugi Condensation of **5b** Using Phthalic Acid

After testing the solubility of ammonium phthalate in various solvents, we chose methanol as the solvent for the Ugi reaction depicted in Scheme 11. Chloroketone **5b** was added to a suspension of ammonium phthalate (4 equiv, 0 °C, 10 min), followed by *t*-butyl isonitrile (1.1 equiv, rt. 16 h). Extractive workup afforded acylaziridine **28** (Scheme 4.13) in 33% yield. However, when the Ugi reaction was repeated using the less nucleophilic trifluoroethanol as solvent, only traces of phthalimide **26** were detected by mass spectrometry. Instead, the major product was hydroxyamide **29**, apparently the result of a 2-component Passerini condensation. The structure of **29** was confirmed by single crystal X-ray analysis (Figure 4.2).



Scheme 4.13 Ugi Reaction of Chloroacetone with Ammonium Phthalate

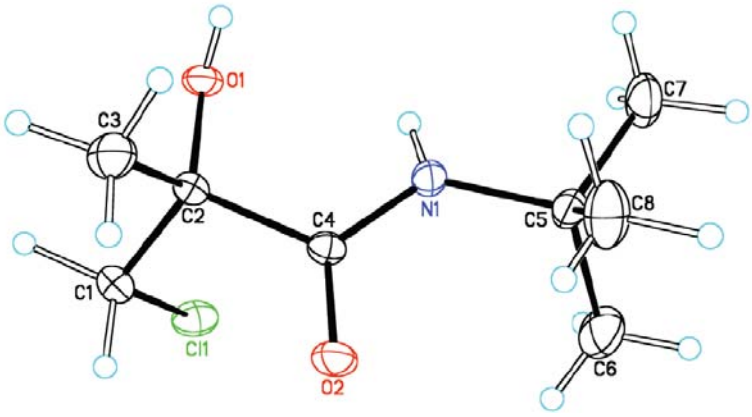
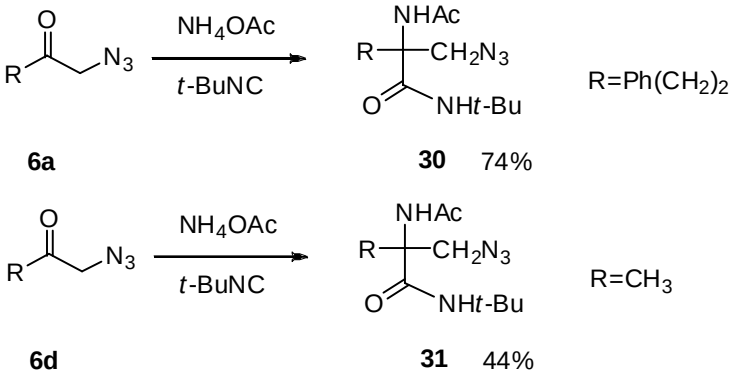


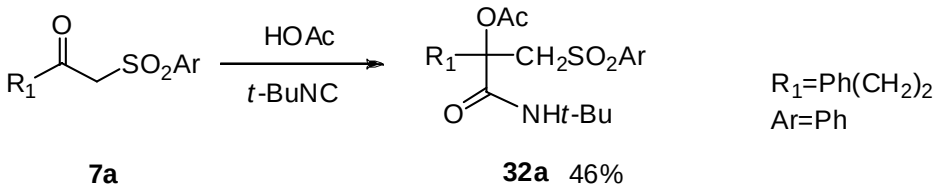
Figure 4.2 ORTEP Diagram of the X-ray Crystal Structure of **29**

The relatively rapid Passerini reaction of **6a** (Figure 4.1) suggested that such azidoketones, although heretofore unstudied in isonitrile-based MCRs, would be good substrates for such complexity-generating processes. Furthermore, alkyl azides are particularly useful components in the synthesis of triazoles and tetrazoles by copper-catalyzed cycloadditions with alkynes using "click" chemistry.[24] As shown in Scheme 4.14, representative Ugi condensations of **6a** and **6d** (R = CH_3) with ammonium acetate and *t*-butyl isonitrile afforded the expected diamides **30** and **31** (Scheme 4.14) in reasonable yield.



Scheme 4.14 Ugi Reaction of Azidoketones **6a, 6d**

We also investigated isonitrile-based MCRs of α-arylsulfonylketones having general structure **7**. Unlike other representative α-substituted ketones in this study, sulfonylketones (also known as β-ketosulfones) are distinguished by their relatively acidic methylene hydrogens and have widespread applications, in the synthesis of disubstituted alkynes,[25] alkenes,[26] allenes,[27] and heterocycles.[28] Some β-ketosulfones function as aromatase inhibitors[29] and also exhibit fungicidal activity.[30] The Passerini condensation of phenylsulfonyl ketone **7a** (Scheme 4.15) with acetic acid and *t*-butyl isonitrile (1 equiv each) reported in the kinetic study (Figure 4.1) proceeded smoothly (rt, 1 d) to afford the expected product **32a** (46% yield) as an inseparable 1:1 mixture with **7a**, based on NMR analysis.



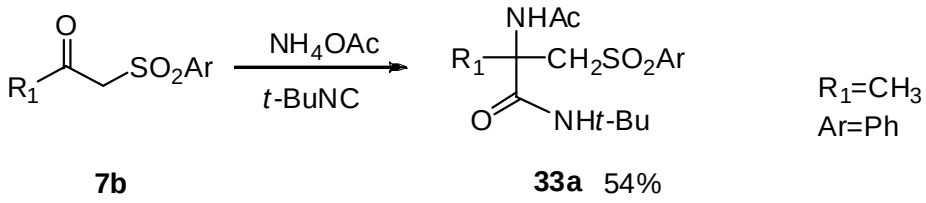
Scheme 4.15 Passerini Reactions with α-Arylsulfonylketones **7**

The process seemed to be general, judging from the representative cases shown in Table 4.5, in which variations to the arylsulfonyl group and to the carbon framework of the ketone were introduced. Unlike **32a**, products **32b-f** were obtained pure after flash chromatography. Interestingly, using 2 equiv of acid and isonitrile shortened the overall reaction time, but failed to improve the yield of product.

Table 4.5 Passerini Reactions with α-Arylsulfonylketones **7**

α-arylsulfonylketones **7**	R_2CO_2H R_2=	R_3NC R_3=	product (yield)
7a R_1=Ph$(CH_2)_2$, Ar=Ph	CH_3	*t*-Bu	**32a** (46%)
7b R_1= CH_3, Ar=Ph	CH_3	*n*-Bu	**32b** (40%)
7b	Ph	*t*-Bu	**32c** (50%)
7b	$(CH_3)_2CH$	*cyclo*-C_6H_{11}	**32d** (69%)
7c R_1= CH_3, Ar=*p*-FC_6H_4	Ph	*cyclo*-C_6H_{11}	**32e** (40%)
7c	Ph	*t*-Bu	**32f** (36%)

A representative Ugi condensation using phenylsulfonyl ketone **7b** with ammonium acetate and *t*-butyl isonitrile was performed as an initial reactivity test, and afforded the expected product **33a** (Scheme 4.16, 54%). However, additional examples summarized in Table 4.6 defined a narrow scope of reactivity.



Scheme 4.16 Ugi Reactions with α-Arylsulfonylketones **7**

Table 4.6 Ugi Reactions with α-Arylsulfonylketones **7**

α-arylsulfonylketones **7**	R_2CO_2H R_2=	R_3NH_2 R_3=	R_4NC R_4=	product (yield)
7b R_1= CH_3, Ar=Ph	CH_3	H	*t*-Bu	**33a** (54%)
7b	Ph	H	*t*-Bu	**33b** (<5%)
7b	CH_3	H	CH_2CO_2Et	**33c** (64%)
7c R_1= CH_3, Ar=*p*-FC_6H_4	CH_3	H	*n*-Bu	**33d** (51%)

In entry 2, the low yield obtained of product **33b** could not be improved by switching the solvent to the more commonly used methanol, and was apparently due to the poor solubility of benzoic acid in either solvent. Attempts to use benzylamine in place of ammonia produced complex mixtures in which neither the Ugi (expected) nor Passerini product could be identified. Generally, the reaction was successful with a number of isonitriles including *t*-butyl or *n*-butyl isonitrile as well as ethyl isocyanoacetate.

4.3 Conclusion

In conclusion, we have shown that numerous α-functionalized ketones having general structures **2-7** can serve as useful carbonyl components in isonitrile-based MCRs, occasionally with unexpected and surprising outcomes. The successful application of Passerini and Ugi condensations to families of ketones **2-7** enhances the utility of these two powerful name reactions, and adds another dimension to the structural complexity that can be achieved using multicomponent reactions.

4.4 Experimental Procedures

Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR were taken on a Varian Mercury-300, Varian Inova-400 or Varian Inova-500 spectrometer as indicated using $CDCl_3$ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and were referenced to TMS (0.00 ppm for ^{1}H NMR) and $CDCl_3$ (77.23 ppm for ^{13}C NMR). IR spectra were obtained on a Mattson Instruments Galaxy Series FT-IR spectrometer and were recorded in wavenumbers (cm^{-1}). Chemicals were obtained from Aldrich, Fluka, Fisher, Lancaster, Mallinckrodt, or Novabiochem and used as received unless specified. Ether was distilled from sodium/benzophenone. Methanol and 2,2,2-trifluoroethanol was distilled from CaH_2.

Representative Procedure for the Passerini Reaction of α-Mesyloxyketones 2.

*Compound **9a**:* α-mesyloxyketone **2a** (48 mg, 0.2 mmol, 1equiv) was added in a 5 mL round bottom flask as solid. It was blanketed in nitrogen, then treated with acetic acid (13 μL, 0.22 mmol, 1.1 equiv) and *t*-butyl isocyanide (25 μL, 0.22 mmol, 1.1 equiv). The resulting homogeneous mixture was stirred at rt under N_2 for 20 h. The product was purified by flash column chromatography (3:7 EtOAc/hexanes, Rf=0.2) to afford **9a** (68 mg, 88%) as a pale yellow oil.

Representative Procedure for the Synthesis of Acyloxy β-lactams.

*Compound **11a**:* sodium hydride (80% mineral oil dispension, 9 mg, 0.3 mmol, 1.5 equiv) was added in a dry 25 mL round bottom flask as solid. It was washed with 1 mL pentane twice, then suspended in 4:1 DCM/DMF (3 ml) under nitrogen at 0 °C. To it was added **9c** solution (82 mg, 0.2 mmol, in 3 mL 4:1 DCM/DMF) drop wise . The reaction mixture was stirred at rt for 2 h. Saturated NH_4Cl (6 mL) was then added with the stirring for 0.5 h at rt. After separating the layers, the aqueous phase was extracted with DCM (5 mL) and the combined organic layers were washed with H_2O (5 mL) and saturated NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated in

vacuo. The crude product was purified by silica gel flash column chromatography (3:7 EtOAc/hexanes, R_f= 0.3), to afford the desired product **11a** as a pale yellow oil.

Representative Procedure for the Ugi Reaction of α-Mesyloxyketones 2 with Primary Amines.

*Compound **15a**:* To a solution of α-mesyloxyketone **2a** (48 mg, 0.2 mmol, 1equiv) in anhydrous 2,2,2-trifluoroethanol (0.5 mL) at 0 °C was added benzylamine (178 μL, 0.8 mmol, 4.0 equiv) dropwise. The reaction mixture was stirred for 10 min at 0 °C, then acetic acid (23 μL, 0.4 mmol, 2.0 equiv) and cyclohexyl isonitrile (27 μL, 0.22 mmol, 1.1 equiv) were added via syringe with stirring. The reaction mixture was then warmed to rt and stirred for 18 h. The solvent was removed *in vacuo.* The residula oil was purified by silica gel flash column chromatography (3:7 EtOAc/hexanes,, R_f= 0.3) to afford **15a** as a white solid (57 mg, 71%)

Representative Procedure for the Synthesis of Di-*O*-acylglyceramides.

*Compound **20b***: A mixture of acetic acid (57 μL, 1.0 mmol) and Cu(acac)2 (2.6 mg, 0.01 mmol, 1 mol %) toluene (2 mL) in a 10 mL round-bottom flask was heated to 60 °C for 10 min under nitrogen. To it was added dropwise a solution of diazoketone **1a** (226 mg, 1.3 mmol, 1.3 equiv) in toluene (2 mL). Once gas evolution was judged complete, the reaction mixture was stirred an additional 5 min, then cooled and concentrated *in* V*acuo*. The oily residue was blanketed in nitrogen, then treated with *iso*butyric acid (140 μL, 1.5 mmol, 1.5 equiv) and *t*-BuNC (170 μL, 1.5 mmol, 1.5 equiv). The resulting reaction mixture was stirred at rt under N2 for 20 h. The product was purified by silica gel flash column chromatography (1:1 EtOAc:hexanes, *Rf*) 0.3) to afford **5b** (338 mg, 90%) as a pale-yellow oil.

Representative Procedure for the Passerini Reaction of α-Sulfonylketones 7.

*Compound **32d***: To a stirred solution under N_2 of freshly dried phenylsulfonylacetone **7b** (67 mg, 0.34 mmol) in CH2Cl2 (0.02 mL, 19 *M*) was added isobutyric acid (37 μL,

0.37 mmol) followed by cyclohexylisonitrile (45.5 μL, 0.37 mmol). The reaction mixture was stirred at rt for four days, then volatile residues were removed under reduced pressure. After TLC analysis,[31] the product was purified by silica gel flash chromatography (2:1 ethyl acetate:hexanes, *Rf*) 0.5) to furnish pure **32d** (92 mg, 69%) as a colorless oil.

Representative Procedure for the Ugi Reaction of α-Sulfonylketones 7.

*Compound **33a***: A solution of NH4OAc (101 mg, 1.31 mmol) and freshly dried phenylsulfonylacetone **7b** (65 mg, 0.33 mmol) in anhydrous 2,2,2-trifluoroethanol (add vol, 0.4 M) under N_2 was stirred at 0 °C for 1 h. The, *t*-butyl isonitrile (41 μL, 0.36 mmol) was added and stirring at rt was continued for two days. Volatiles were removed under reduced pressure, and after TLC analysis,[31] the crude oily product was purified by silica gel flash chromatography (10:1 ethyl acetate: hexanes, Rf 0.3) to furnish pure **33a** (60 mg, 54% yield) as a white solid (mp 175-176 °C).

IR, MS and Other Physical Characterization Data for New Products

*Mesylate **9a**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a pale yellow oil (68 mg, 88%): IR (CH_2Cl_2) 3435(s), 2964(s), 1748(s), 1672(s), 1523(s); CIMS (methane) *m/z* 386 (M+H), 344, 326, 290, 266.

*Mesylate **9b**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a pale yellow oil (82%): IR (CH_2Cl_2) 3399(s), 2934(s), 1725(s), 1655(s), 1520(s); CIMS (methane) *m/z* 474 (M+H), 396, 378, 352, 256.

*Mesylate **9c**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a clear oil (80%): IR (CH_2Cl_2) 3399(s), 2934(s), 2854(s), 1748(s), 1665(s), 1526(s); CIMS (methane) *m/z* 412 (M+H), 370, 334, 316, 256.

*Mesylate **9d**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a white solid (91%): IR (CH_2Cl_2) 3349(s), 2934(s), 2851(s), 1748(s), 1659(s), 1532(s); CIMS (methane) *m/z* 406 (M+H), 364, 346, 310, 268.

*Mesylate **9e** :* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a pale yellow oil (80%): IR (CH_2Cl_2) 3405(s), 2934(s), 2868(s), 1715(s), 1655(s), 1532(s); CIMS (methane) *m/z* 426 (M+H), 376, 348, 330, 208.

*Mesylate **9f**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a pale yellow oil (18%): IR (CH_2Cl_2) 3380(s), 3059(m), 2931(s), 2850(s), 1752(s), 1668(s),1521(s); CIMS (methane) *m/z* 384 (M+H), 342, 324, 288, 246.

*Tosylate **10a**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a pale yellow oil (99%): IR (CH_2Cl_2) 3438(s), 3388(m), 2967(s), 2924(s), 1725(s), 1685(s),1519(s); CIMS (methane) *m/z* 524 (M+H), 447, 402, 370, 352.

*Tosylate **10b**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a pale yellow oil (97%): IR (CH_2Cl_2) 3442(s), 3385(s), 3342(s,)2931(s), 2854(s), 1725(s), 1669(s),1516(s); CIMS (methane) *m/z* 550 (M+H), 378, 350, 286.

*Tosylate **10c**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a pale yellow oil (97%): IR (CH_2Cl_2) 3396(s), 3339(s), 2927(s), 2851(s), 1745(s), 1659(s); CIMS (methane) *m/z* 482 (M+H), 440, 422, 338, 310, 268.

*Tosylate **10d**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as

a pale yellow oil (100%): IR (CH_2Cl_2) 3332(s), 2927(s), 2854(s), 1728(s), 1662(s),1526(s); CIMS (methane) *m/z* 544 (M+H), 447, 400, 372.

*Tosylate **10e**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a clear oil (80%): IR (CH_2Cl_2) 3442(s), 3392(s), 2931(s), 2857(s), 1742(s), 1675(s),1526(s); CIMS (methane) *m/z* 440 (M+H), 398, 380, 268, 244.

*Tosylate **10f**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a white solid (28%): IR (CH_2Cl_2) 3283(s), 2914(s), 2847(s), 1728(s), 1678(s),1652(s); CIMS (methane) *m/z* 522 (M+H), 504, 454, 400, 378, 350.

*β-Lactam **11a**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a pale yellow oil (62%): IR (CH_2Cl_2) 3053(s), 2927(s), 2857(s), 1751(s); CIMS (methane) *m/z* 344, 316 (M+H), 274, 246, 112.

*β-Lactam **11b**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.4), to afford the desired product as a pale yellow oil (46%): IR (CH_2Cl_2) 2967(s), 1758(s), 1725(s),1599(s); CIMS (methane) *m/z* 380, 352 (M+H), 296, 268.

*β-Lactam **11c**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.4), to afford the desired product as a pale yellow oil (59%): IR (CH_2Cl_2) 2930(s), 2851(s), 1755(s), 1719(s), 1277(s); CIMS (methane) *m/z* 406, 378 (M+H), 352, 267.

*β-Lactam **11d**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a clear oil (64%): IR (CH_2Cl_2) 2920(s), 2864(s), 1754(s), 1453(s), 1373(s); CIMS (methane) *m/z* 338, 310 (M+H), 268, 250.

β-Lactam ***11e****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.5), to afford the desired product as a clear oil (56%): IR (CH_2Cl_2) 2927(s), 2854(s), 1755(s), 1722(s); CIMS (methane) *m/z* 400, 372 (M+H), 344, 261.

Ugi Product ***15a****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a white solid (71%): IR (CH_2Cl_2) 3350(s), 2931(s), 1740(s), 1664(s), 1516(s); CIMS (methane) *m/z* 423 (M+H), 363, 296, 258.

Ugi Product ***15b****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.4), to afford the desired product as a white solid (66%): IR (CH_2Cl_2) 3367(s), 2936(s), 1734(s), 1660(s), 1512(s); CIMS (methane) *m/z* 401 (M+H), 383, 339, 313, 284.

Ugi Product ***15c****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a white solid (67%): IR (CH_2Cl_2) 3362(s), 2930(s), 1722(s), 1670(s), 1514(s); CIMS (methane) *m/z* 453 (M+H), 435, 362, 352.

Ugi Product ***15d****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.4), to afford the desired product as a white solid (61%): IR (CH_2Cl_2) 3365(s), 2930(s), 1734(s), 1665(s), 1514(s); CIMS (methane) *m/z* 395 (M+H), 377, 307, 268, 252.

Ugi Product ***15e****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a white solid (39%): IR (CH_2Cl_2) 3388(s), 2970(s), 2933(s), 1735(s), 1652(s), 1529(s); CIMS (methane) *m/z* 369 (M+H), 351, 314, 278, 213.

Ugi Product ***15f****:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as

a white solid (74%): IR (CH_2Cl_2) 3352(s), 3055(s), 2985(s), 1740(s), 1672(s), 1514(s); CIMS (methane) *m/z* 307 (M+H), 247, 206.

*Ugi Product **17a**:* The crude product was purified by silica gel flash column chromatography (1:1ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a pale yellow solid (67%): IR (CH_2Cl_2) 3422(s), 3329(s), 2924(s), 2851(s), 1742(s), 1649(s), 1526(s); CIMS (methane) *m/z* 493, 465 (M+H), 403, 375.

*Product **18a**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a clear oil (60%): IR (CH_2Cl_2) 3346(s), 2924(s), 2850(s), 1648(s), 15525(s); CIMS (methane) *m/z* 381 (M+H), 349, 282, 254.

*Ugi Product **21a**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a white solid (85%): IR (CH_2Cl_2) 3425(s), 3338(s), 3055(s), 2985(s), 1672(s), 1497(s); CIMS (methane) *m/z* 235 (M+H), 199, 162.

*Ugi Product **21b**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.1), to afford the desired product as a white solid (85%): IR (CH_2Cl_2) 3425(s), 3055(s), 1670(s), 1506(s); CIMS (methane) *m/z* 261 (M+H), 225, 162.

*Passerini Product **22:*** The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.5), to afford the desired product as a pale yellow oil (10%): IR (CH_2Cl_2) 3439(s), 3055(s), 2985(s), 1749(s), 1676(s), 1421(s); CIMS (methane) *m/z* 262 (M+H), 220, 202.

*Ugi Product **28**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a clear oil (33%): IR (CH_2Cl_2) 3352(s), 3053(s), 2987(s), 1711(s), 1668(s), 1648(s), 1638(s); CIMS (methane) *m/z* 305 (M+H), 287, 249, 205.

*Ugi Product **29**:* The crude product was purified by silica gel flash column chromatography (1:1 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a pale yellow oil (49%): IR (CH_2Cl_2) 3389(s), 2970(s), 2934(s), 1735(s), 1652(s); CIMS (methane) *m/z* 194 (M+H), 178, 166, 138.

*Ugi Product **30**:* The crude product was purified by silica gel flash column chromatography (3:7 ethyl acetate: hexanes, R_f= 0.3), to afford the desired product as a pale yellow oil (74%): IR (CH_2Cl_2) 3442(s), 3026(s), 2967(s), 2107(s), 1748(s), 1679(s), 1523(s); CIMS (methane) *m/z* 333 (M+H), 305, 245.

*Ugi Product **31**:* The crude product was purified by silica gel flash column chromatography (7:3 ethyl acetate: hexanes, R_f= 0.2), to afford the desired product as a white solid (44%): IR (CH_2Cl_2) 3422(s), 3363(s), 3053(s), 2981(s), 2107(s), 1675(s); CIMS (methane) *m/z* 242 (M+H), 214, 200,169.

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(31) In cases where the product had the same R_f value as the starting ketone, the crude product was dissolved in CH_2Cl_2 and washed with 0.2 M NaOH saturated with NaCl. The aqueous layer was back-extracted twice with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated prior to chromatography.

CHAPTER FIVE

Future Direction: Synthesis of Caged Gamma-Aminobutyric Acid and Caged Carbamoylcholine Chloride

5.1 Background

The protection of biological molecules by conversion into inactive photolabile derivatives (caged precursors) has received increased attention in cell biology. Because their deprotection only requires light and very mild conditions, caging groups are widely used in the controlled delivery of bioactive molecules with high temporal and spatial precision without physically disturbing biological systems.[1]

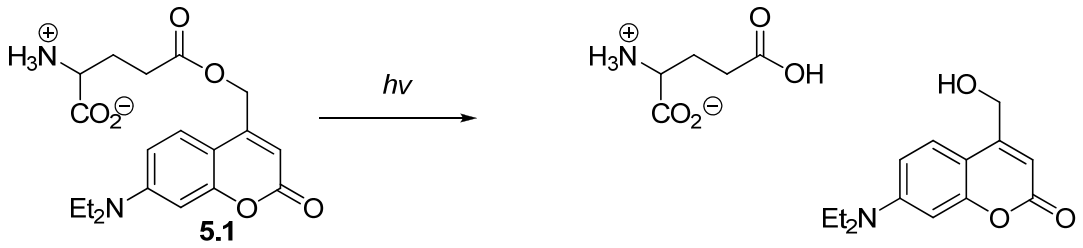
During the last 40 years, caged neurotransmitters have become a powerful tool in transient kinetic investigations of the mechanism of action of neurotransmitter receptors.[2] Neurotransmitters are small organic molecules essential for the transmission of signals in the central nervous system (CNS). As chemical signal carriers, neurotransmitters are used to relay, amplify and modulate electrical signals between neurons and other cells by reacting with neurotransmitter receptors. These neurotransmitter receptors exhibit distinct kinetic and pharmacological profiles, which are important to the study of many neurological disorders in the CNS.

To investigate the kinetics and mechanism of neurotransmitter receptors, and how mutations affect receptor ligand interactions, biologically inert caged neurotransmitter precursors have been developed by covalently bonding neurotransmitters to photolabile protecting groups. The rapid release (in the microsecond domain) of biologically active neurotransmitters by photolysis is capable of providing the time resolution necessary for the investigation of the fast processes involved in activation and inhibition of neurotransmitter receptors.[3]

Our effort focused on developing caged neurotransmitters for the two most common neurotransmitter receptors, the gamma-aminobutyric acid (GABA) receptor and the acetylcholine receptor. GABA is an amino acid and the main inhibitory neurotransmitter in the CNS. GABA receptors have been linked to epilepsy, sleep disorders, and Parkinson's disease.[2] Acetylcholine is an ester of acetic acid with choline, and functions both in the CNS and the peripheral nervous system (PNS) as a

neuromodulator. The acetylcholine receptor has been associated with myasthenia gravis and Alzheimer's disease.[4]

Traditional caged neurotransmitters are released upon irradiation with UV-light source, which requires expensive lasers and special safety precautions. Another important drawback of UV sensitive caged neurotransmitters is that only 2 or 3 measurements can be made on each cell before the cell dies from the damage caused by high-energy UV exposure. To circumvent these problems, Hess et al developed a new caging group for carboxyl-containing neurotransmitters that is activated in the visible wavelength region. 7-(*N*,*N*-diethylamino)-4-(hydroxymethyl) coumarin (DECM) caged glutamate **5.1** was synthesized and photolyzed rapidly and efficiently at 400 nm (Scheme 5.1).[3]



Scheme 5.1 Photolysis of DECM-Caged Glutamate

Compound **5.1** was successfully used in a study of the GluR6 glutamic acid receptor. Both the DECM-glutamate and its photolytic byproducts were shown to be biologically inert to the glutamic acid receptors. To study GABA receptors with the same technique, the corresponding caged GABA precursor **5.2** (Figure 5.1) was recently synthesized. Compound **5.2** released GABA upon photolysis; however, **5.2** interfered with the channel-opening process of the wild-type GABA receptor.

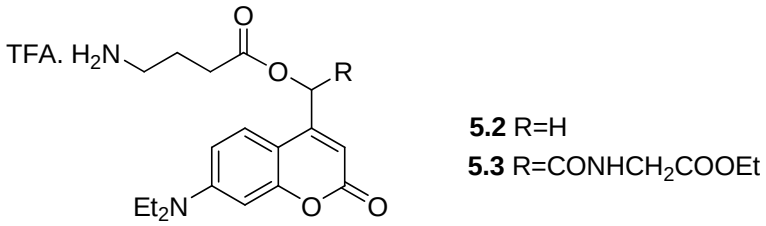
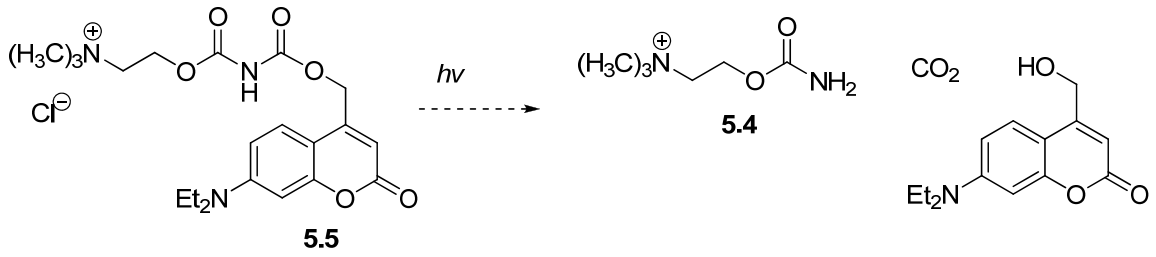


Figure 5.1 Caged GABA Compounds of Interest

To avoid this undesired biological activity, we devised an alternative multicomponent route to a family of carboxy-substituted DECM-GABA derivatives, represented by compound **5.3**. Preliminary biological study of compound **5.3** showed a high quantum yield for decaging using 400 nm light. Moreover, both **5.3** and its photolysis byproducts were inert towards the GABA receptors.

Caging acetylcholine posed a challenge because it lacked a functional group that could be chemically modified. A stable cholinergic agonist, carbamoylcholine chloride **5.4** (Scheme 5.2), was chosen in the acetylcholine receptor study. Carbamoylcholine, also known as carbachol (marketed under the brand names Carbastat, Carboptic, Isopto Carbachol, Miostat), is a choline ester and a positively charged quaternary ammonium compound that binds and activates the acetylcholine receptor.[5]



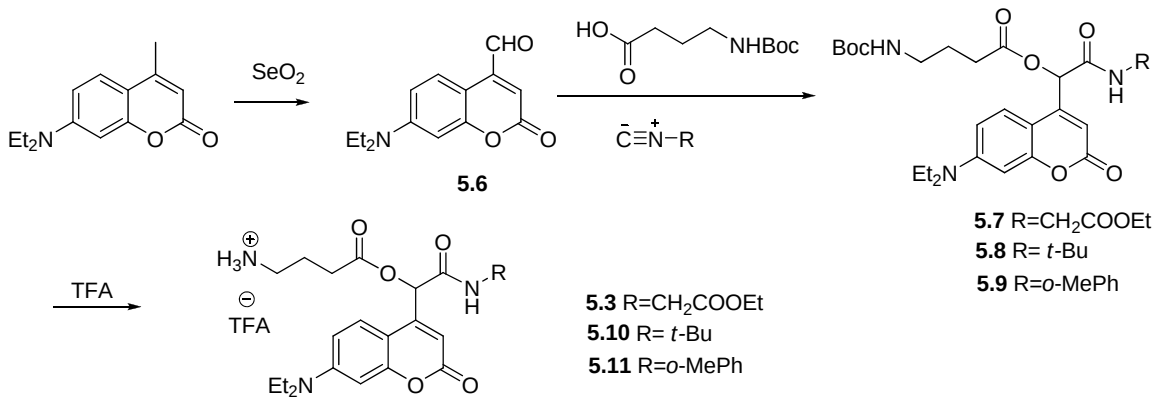
Scheme 5.2 Caged Carbamoylcholine Chloride

Prior to our study, there was no published report of a DECM caged carbamate or amide. Previous investigations suggested that an ester linkage was desired between the DECM and carbamoylcholine to enable decaging in high quantum yield. However, a

direct ester linkage between carbamoylcholine and DECM was not possible in this case. Therefore, an indirect linkage was designed between the carbamoylcholine and DECM caging group through an imidodicarbonate (Scheme 5.2). Our expectation was that after photolysis, the resulting hydrogen iminodicarbonate would afford carbamoylcholine by releasing CO_2. Therefore a highly convergent one-pot synthesis of the DECM caged carbamoylcholine chloride **5.5** was developed to test this hypothesis.

5.2 Synthesis of Caged GABA

A multicomponent approach to the target compound was devised using the Passerini reaction, which affords α-acyloxyesters from the condensation of simple aldehydes with carboxylic acids and isonitriles. The known aldehyde **5.6**, prepared by selenium dioxide oxidation of 7-(*N*,*N*-diethylamino)-4-methyl coumarin,[2] underwent a smooth 3-component condensation with ethyl isocyanoacetate and BOC-protected GABA to afford the acyloxydiester **5.7** in 96% yield (Scheme 5.3). Similar reaction of **5.7** and BOC-protected GABA with *t*-butyl isonitrile and *o*-tolylisonitrile afforded caged GABA derivatives **5.8** and **5.9**, respectively. Compounds **5.7-5.9** were purified by flash chromatography in the dark for full structural characterization.



Scheme 5.3 Synthesis of Caged GABA Compounds

The desired caged GABA compounds **5.3, 5.10**, and **5.11** were then obtained by removing the BOC protecting group upon treatment with TFA. Residual free GABA was removed by flash chromatography in the absence of light.

5.3 Synthesis of Caged Carbamoylcholine Chloride

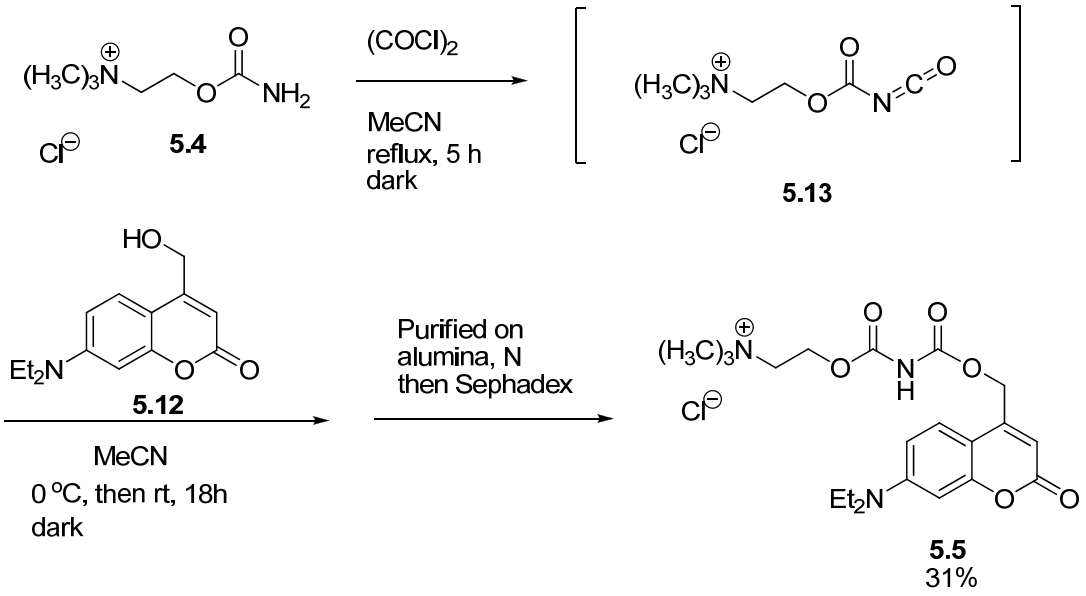
A highly convergent one-pot approach from the known alcohol **5.12** to the target compound **5.5** was developed (Scheme 5.4). The alcohol **5.12** was prepared by reduction of DECM aldehyde **5.6** with sodium borohydride in EtOH.[2]

Carbamates were known to form the corresponding acylisocyanate upon treatment with oxalyl chloride. The resulting isocyanates are highly reactive intermediates and usually used immediately in *situ* to couple with nucleophiles such as alcohols or amines. In most cases, this reaction was carried out in DCM or 1,2 dichloroethane.[6] However, carbamoylcholine **5.4**, as a quaternary ammonium salt, was soluble only in water, dimethylformamide and dimethyl sulfoxide, none of which was compatible with oxalyl chloride. After careful screening of various organic solvents and conditions, the carbamoylcholine acylisocyanate **5.13** was prepared by reacting carbamoylcholine chloride **5.4** with oxalyl chloride in refluxing MeCN for 6 h.

Excess oxalyl chloride and solvent was then immediately removed in *vacuo* by continuously pumping the reaction flask with a standard high vacuum oil pump for 30 min. The complete removal of oxalyl chloride was necessary to ensure good yield because oxalyl chloride reacts more readily with alcohol **5.12** than isocyanate **5.13** does and the HCl generated in such side reactions further diminishes the yield by catalyzing the decomposition of the imidodicarbonate **5.5**. After pumping, the resulting crude grey solid **5.13** was dissolved again in fresh MeCN and used immediately in the next step without purification.

Compound **5.13** underwent a smooth coupling reaction with the alcohol **5.12** to afford the desired imidodicarbonate **5.5**. After removing solvent in *vacuo*, the crude **5.5**

as a black solid was purified by tandem flash column chromatography in the dark to yield pure **5.5** as a yellow solid for full structural characterization.



Scheme 5.4 Synthesis of Caged Carbamoylcholine Chloride **5.5**

5.4 Conclusion

Photolabile DECM-caged GABA compounds (**5.3**, **5.10**, **5.11**) and carbamoylcholine chloride **5.5** were synthesized from readily available starting materials. Care was taken to protect the caged neurotransmitters and their derivatives from light, particularly when handling aqueous solutions. The caged compounds were sufficiently soluble in water and buffers and were stable in the dark when stored cold. Upon exposure to visible light, both caged precursors released bioactive neurotransmitter rapidly and efficiently. Caged carbamoylcholine **5.5** represents the first DECM caged carbamate and the first DECM caged agonist for acetylcholine receptor. This new method has the

potential to introduce photolabile protecting groups that can be deprotected in the visible wavelength region.

Caged neurotransmitters are important tools in elucidating the mechanism of neurotransmitter receptors. On the basis of their mechanism of action, therapeutic agents are being developed to alleviate symptoms caused by dysfunctional receptors in many neurological disorders. With these visible-light-sensitive caged neurotransmitters, simple-to-use, readily available inexpensive light sources can now be applied in transient kinetic investigations of a wide range of neurotransmitter receptors, thereby opening up this important field to an increasing number of investigators.

5.5 Experimental Procedures

^{1}H NMR and ^{13}C NMR were taken on a Varian Inova-400 or Varian Inova-500 spectrometer as indicated using D_2O and $CDCl_3$ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and were referenced to TMS (0.00 ppm for ^{1}H NMR), H_2O (4.80ppm for ^{1}H NMR) and $CDCl_3$ (77.23 ppm for ^{13}C NMR). IR spectra were obtained on a Thermo Nicolet Avatar 370 DTGS spectrometer and were recorded in wavenumbers (cm^{-1}). Chemicals were obtained from Aldrich, Fluka, Fisher, Mallinckrodt and used as received unless specified.

Representative experimental procedure for the synthesis of Passerini compounds 5.7, 5.8, 5.9.

*Compound **5.7***: coumarin aldehyde (50 mg, 0.2 mmol, 1 equiv) was dissolved with 0.2 mL DCM in a 5 mL round bottom flask. It was blanketed in nitrogen and covered with Al foil. To it was added 4-(Boc-amino)butyric acid (40 mg, 0.2 mmol, 1 equiv) and ethyl isocyanoacetate (22 μL, 0.2 mmol, 1 equiv). The resulting homogeneous mixture was stirred at rt in dark for 18 h. The product was concentrated in *vacuo* and purified by flash column chromatography in dark (1:1 EtOAc/hexanes, then EtOAc, Rf=0.1) to afford **5.7** (101 mg, 90%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, 1 H), 7.61 (d, 1 H), 6.56 (d, 1 H), 6.40 (s, 1 H), 6.33(s, 1 H), 6.19 (s, 1 H), 5.26 (t, 1 H), 4.04 (dd, 2 H),

3.92 (td, 2 H), 3.33 (dd, 2 H), 3.15 (m, 1 H), 3.06 (m, 1 H), 2.51 (m, 1 H), 2.40 (m, 1 H), 1.80 (m, 1 H) 1.71 (m, 1 H), 1.33 (s, 9 H), 1.09 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.03, 168.90, 166.90, 161.63, 156.47, 156.21, 149.35, 126.41, 108.79, 107.65, 97.27, 79.05, 71.11, 61.14, 44.70, 41.04, 38.91, 30.62, 28.24, 25.42,13.98, 12.31; IR (CH_2Cl_2) 3336(s), 2977(s), 2937(s), 1742(s), 1682(s), 1619(s), 1596(s); MS (ESI) *m/z*: 562.2 (M+H), 506.2.

*Compound **5.8***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 1 H), 6.61 (d, 1 H), 6.48 (d, 1 H), 6.33 (d, 1 H), 6.17 (s, 1 H), 6.12 (s, 1 H), 4.79 (s, 1 H), 3.42 (dd, 4 H), 3.20 (m, 2 H), 2.55 (m, 2 H), 1.88 (m, 2 H), 1.44 (s, 9 H), 1.34 (s, 9 H), 1.20 (t, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29, 169.88, 169.87, 165.36, 162.11, 156.74, 156.28, 150.95, 150.48, 126.77, 109.94, 109.01, 106.87, 106.48, 97.68, 79.49, 71.79, 52.15, 44.89, 39.55, 31.32, 28.70, 28.53, 25.61, 12.58; IR (CH_2Cl_2) 3345(s), 3066(m), 2980(s), 2927(s), 1708(s), 1615(s); MS (ESI) *m/z*: 532.2 (M+H), 476.2, 338.2.

*Compound **5.9***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1 H), 7.78 (d, 1 H), 7.42 (d, 1 H), 7.06-7.20 (m, 3 H), 6.59 (d, 1 H), 6.46 (d, 2 H), 6.27 (s, 1 H), 4.82 (s, 1 H), 3.40 (dd, 4 H), 3.29 (s, 1 H), 3.17 (m, 1 H), 2.62 (m, 1 H), 2.54 (m, 1 H), 2.19 (s, 3 H), 1.95 (m, 1 H), 1.80 (m, 1 H), 1.33 (s, 9 H), 1.19 (t, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.10, 165.27, 162.26, 156.95, 156.81, 151.17, 150.17, 134.80, 132.42, 130.87, 127.13, 126.84, 126.81, 125.45, 109.28, 107.45, 106.65, 97.96, 95.41, 79.98, 72.31, 45.25, 39.59, 31.39, 28.75, 26.22, 18.27, 12.99; IR (CH_2Cl_2) 3312(s), 2970(s), 2937(s), 1647(s), 1711(s), 1612(s), 1592(s); MS (ESI) *m/z*: 566.3 (M+H), 532.3.

Representative experimental procedure for the synthesis of DECM caged GABA compounds 5.3, 5.9, 5.10

*Compound **5.3***: Passerini product **1** (20 mg, 0.036 mmol, 1 equiv) was dissolved with 0.5 mL chloroform in a 5 mL round bottom flask under nitrogen and the flask was wrapped with Al foil. To it was added TFA (100 µL, 2.7 mmol, 30 equiv) via syringe. The resulting homogeneous mixture was stirred at rt in dark for 18 h. The concentrated crude

compound was dissolved in H_2O (0.2 ml) in dark and transferred onto silica column. It was washed with H_2O (20 mL) followed by acetonitrile (20 mL), then eluted with acetonitrile with 0.5% v/v TFA (20 mL). The last eluent was concentrated and lyophilized to afford **5.3** (12.3 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, D_2O) δ 8.07 (d, 1 H), 7.57 (d, 1 H), 7.47 (dd, 1 H), 6.74 (s, 1 H), 6.43 (s, 1 H), 3.98 (dd, 2 H), 3.91 (s, 2 H), 3.59 (dd, 4 H), 2.93 (t, 2 H), 2.60 (m, 2 H), 1.89 (m, 2 H), 1.58-1.75 (m, 3 H), 1.01 (m, 9 H); ^{13}C NMR (125 MHz, D_2O) δ 172.54, 170.95, 168.43, 161.75, 154.21, 148.47, 140.06, 128.30, 118.88, 118.46, 117.76, 117.47, 115.15, 112.11, 71.98, 62.61, 54.07, 41.58, 38.66, 30.35, 21.88, 13.34, 9.77; IR (neat) 3080(s), 2980(s), 2951(s), 1748(s), 1668(s), 1615(s); MS (ESI) *m/z*: 462 (M+), 377.1.

*Compound **5.10***: ^{1}H NMR (500 MHz, D_2O) δ 8.12 (d, 1 H), 7.65 (d, 1 H), 7.55 (dd, 1 H), 6.76 (s, 1 H), 6.36 (s, 1 H), 3.70 (dd, 4 H), 3.03 (t, 2 H), 2.73 (m, 2 H), 2.00 (m, 2 H), 1.28 (s, 9 H), 1.12 (t, 6 H); ^{13}C NMR (125 MHz, D_2O) δ 172.85, 166.63, 162.05, 154.26, 148.87, 140.25, 127.79, 118.52, 118.19, 117.64, 116.75, 115.32, 111.83, 72.50, 72.46, 53.83, 52.56, 38.67, 30.42, 27.58, 21.96, 9.86; IR (nujol) 1735(s), 1692(s), 1625(s), 1376(s); MS (ESI) *m/z*: 432.2 (M+), 347.1, 216.6.

*Compound **5.11***: ^{1}H NMR (500 MHz, D_2O) δ 8.26 (d, 1 H), 7.69 (d, 1 H), 7.58 (dd, 1 H), 7.2-7.3 (m, 3 H), 7.11 (d, 1 H), 6.94 (s, 1 H), 6.68 (s, 1 H), 3.70 (dd, 4 H), 3.06 (t, 2 H), 2.73 (m, 2 H), 2.03 (m, 2 H), 2.00 (s, 3 H), 1.12 (t, 6 H); ^{13}C NMR (125 MHz, D_2O) δ 172.88, 167.56, 161.99, 154.42, 135.24, 133.18, 131.13, 128.62, 128.15, 127.06, 126.99, 118.71, 117.47, 112.00, 72.50, 53.91, 38.69, 30.44, 21.99, 16.84, 9.88; IR (neat) 3373(s), 2973(s), 1748(s), 1665 (s), 1422(s); MS (ESI) *m/z*: 466.2 (M+), 381.1.

Experimental procedure for the synthesis of DEAM caged carbamoylcholine chloride product 5.5.

*Compound **5.5***: Carbamoylcholine chloride (50 mg, 0.275 mmol, 3.5 equiv) was suspended with fresh acetonitrile (0.2 mL) in a 10 mL round bottom flask under nitrogen and stirred for 5 min at rt. To it was added oxalyl chloride (100 μL, 1.16 mmol, 15 equiv)

via syringe. Gas was formed. The mixture was refluxed at 80 °C for 5 hr under N_2 yielding a brown homogeneous mixture. Solvent and excess oxalyl chloride was removed by vacuum pump, resulting light brown foam/solid. The solid was dissolved in acetonitrile (0.5 mL). Color darkened and the reaction flask was wrapped with Al foil and cooled in ice bath. To it was added coumarin alcohol (20 mg, 0.08 mmol, 1equiv) in acetonitrile (0.5 mL). The mixture was stirred at rt in dark for 18 h. The crude product was concentrated by vacuum pump and the resulting black solid was extracted with H_2O (3x 1 mL). The aqueous extracts were combined and lyophilized in a foil-covered flask to afford brown solid (~ 200mg). The solid was dissolved in MeOH (0.2 ml) in dark and transferred onto alumina column (Neutral, Activity I, 10 mL). It was eluted with acetone (50mL) followed by MeOH (50 mL). MeOH fractions with positive UV confirmation were combined and concentrated in *vacuo*. The resulting yellow/brown solid was further purified by second flash chromatography (Sephadex LH-20, H_2O). The eluents that were UV positive were concentrated and lyophilized to afford **5.5** (11.3 mg, 31%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-D_6) δ 7.45 (d, 1 H), 6.69 (dd, 1 H), 6.55 (d, 1 H), 6.06 (s, 1 H), 5.34 (s, 2 H), 4.50 (s, 2 H), 3.65 (m, 2 H), 3.43 (q, 4 H), 3.31 (s, 9 H), 1.12 (t, 3 H); ^{1}H NMR (500 MHz, CD_3OD) δ 7.48 (d, 1 H), 6.75 (dd, 1 H), 6.56 (d, 1 H), 6.11 (s, 1 H), 5.40 (s, 2 H), 4.63 (s, 2 H), 3.76 (m, 2 H), 3.49 (q, 4 H), 3.24 (s, 9 H), 1.89 (t, 3 H);^{13}C NMR (125 MHz, CD_3OD) δ 170.44, 164.49, 157.68, 152.83, 152.72, 126.25, 110.63, 107.07, 105.96, 98.44, 66.18, 63.71, 60.33, 54.69, 45.78, 12.85; IR (neat) 3362(s), 2973(s), 1798(s), 1708 (s), 1602 (s); MS (ESI) *m/z*: 419.8 (M+), 229.9.

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